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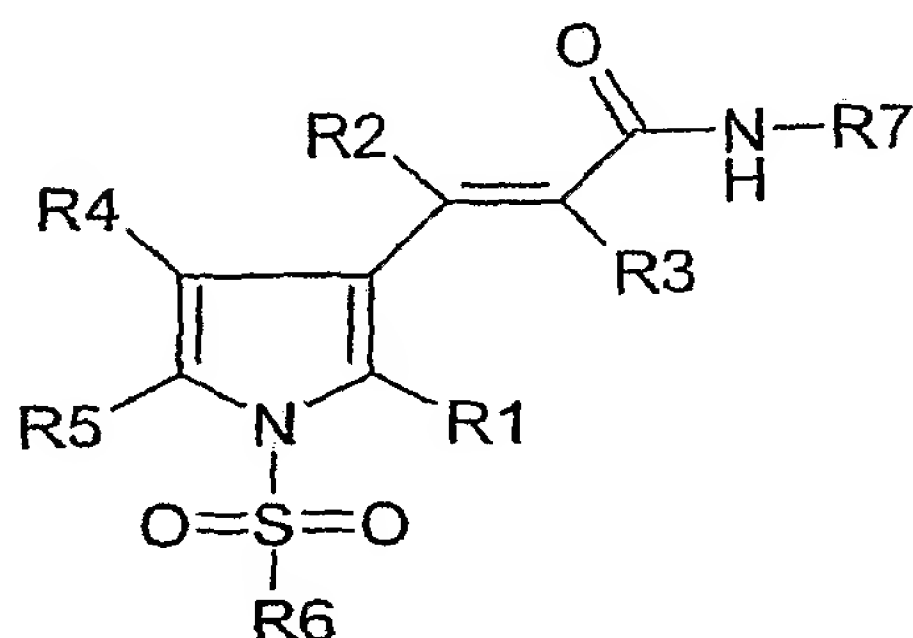
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(54) Title: SULPHONYLPYRROLE HYDROCHLORIDE SALTS AS HISTONE DEACETYLASES INHIBITORS



(I)

(57) Abstract: Compounds of formula I, in which R1, R2, R3, R4, R5, R6 and R7 have the meanings indicated in the description, as well as salts thereof are novel effective HDAC inhibitors. In more detail, this invention refers to salts of a compound selected from (E)-(E)-N-hydroxy-3-(1-[4-((2-(1H-indol-2-yl)-ethyl)-methyl-amino)-methyl)-benzenesulfonyl]-1H-pyrrol-3-yl)-acrylamide, (E)-3-[1-(4-dimethylaminomethyl-benzenesulfonyl)-1H-pyrrol-3-yl]-N-hydroxy-acrylamide, and (E)-N-hydroxy-3-[1-(5-pyridin-2-yl-thiophene-2-sulfonyl)-1H-pyrrol-3-yl]-acrylamide with hydrochloric acid, their hydrates and to crystalline forms of these salts and hydrates.

## SULPHONYLPYRROLE HYDROCHLORIDE SALTS AS HISTONE DEACETYLASES INHIBITORS

### Field of application of the invention

The invention relates to novel N-sulphonylpyrrole derivatives, which are used in the pharmaceutical industry for the production of pharmaceutical compositions.

The invention further relates to certain crystalline salts of these N-sulphonylpyrrole derivatives, which are used in the pharmaceutical industry for the production of pharmaceutical compositions.

### Known technical background

Transcriptional regulation in cells is a complex biological process. One basic principle is regulation by posttranslational modification of histone proteins, namely histone proteins H2A/B, H3 and H4 forming the octameric histone core complex. These complex N-terminal modifications at lysine residues by acetylation or methylation and at serine residues by phosphorylation constitute part of the so called "histone code" (Strahl & Ellis, Nature 403, 41-45, 2000). In a simple model, acetylation of positively charged lysine residues decreases affinity to negatively charged DNA, which now becomes accessible for the entry of transcription factors.

Histone acetylation and deacetylation is catalysed by histone acetyltransferases (HATs) and histone deacetylases (HDACs). HDACs are associated with transcriptional repressor complexes, switching chromatin to a transcriptionally inactive, silent structure (Marks et al. Nature Cancer Rev 1, 194-202, 2001). The opposite holds true for HATs which are associated with transcriptional activator complexes. Three different classes of HDACs have been described so far, namely class I (HDAC 1-3, 8) with Mr = 42-55 kDa primarily located in the nucleus and sensitive towards inhibition by Trichostatin A (TSA), class II (HDAC 4-7, 9, 10) with Mr = 120-130kDa and TSA sensitivity and class III (Sir2 homologues) which are quite distinct by their NAD<sup>+</sup> dependency and TSA insensitivity (Ruijter et al. Biochem.J. 370, 737-749, 2003; Khochbin et al. Curr Opin Gen Dev 11, 162-166, 2001; Verdin et al. Trends Gen 19, 286-293, 2003). HDAC 11 with Mr = 39kDa was cloned recently and displayed homology to class I and II family members (Gao et al. J Biol Chem 277,25748-25755, 2002). HATs and HDACs exist in large complexes together with transcription factor and platform proteins in cells (Fischle et al. Mol Cell 9, 45-47, 2002). Surprisingly, only about 2% of all genes are regulated by histone acetylation (von Lint et al. Gene Expression 5, 245-253, 1996). New studies with SAHA in multiple myeloma cells showed that these transcriptional changes can be grouped into distinct functional gene classes important for eg regulation of apoptosis or proliferation (Mitsiades et al. Proc Natl Acad Sci 101, pp540, 2004). Substrates different to histone proteins exist. For HDACs these include transcription factors like p53 and TFII E / or chaperones like Hsp90 (Johnstone & Licht, Cancer Cell 4, 13-18, 2003). Therefore the correct name for HDACs would be lysine-specific protein deacetylases. As a consequence of these findings, inhibitors of HDACs effect not only chromatin structure and gene transcription but also protein function and stability by regulating protein acetylation in general. This function of HDACs in

protein acetylation might also be important for understanding of immediate gene repression by treatment with HDIs (von Lint et al. *Gene Expression* 5, 245-253, 1996). In this regard, proteins involved in oncogenic transformation, apoptosis regulation and malignant cell growth are of particular importance.

Different publications highlight the importance of histone acetylation for cancer development (reviewed by Kramer et al. *Trends Endocrin Metabol* 12, 294-300, 2001; Marks et al. *Nature Cancer Rev* 1, 194-202, 2001). These diseases include

- (i) mutations of the HAT cAMP response element binding protein (CBP) associated with Rubinstein-Taybi syndrome, a cancer predisposition (Murata et al. *Hum Mol Genet* 10, 1071-1076, 2001),
- (ii) aberrant recruitment of HDAC1 activity by transcription factors in acute promyelocytic leukemia (APL) by the PML-retinoic acid receptor  $\alpha$  fusion gene (He et al. *Nat genet* 18, 126-135, 1998)
- (iii) aberrant recruitment of HDAC activity by the overexpressed BCL6 protein in non-Hodgkins lymphoma (Dhordain et al. *Nucleic Acid Res* 26, 4645-4651, 1998) and finally
- (iv) aberrant recruitment of HDAC activity by the AML-ETO fusion protein in acute myelogenous leukemia (AML M2 subtype; Wang et al. *Proc Natl Acad Sci USA* 95, 10860-10865, 1998). In this AML subtype, the recruitment of HDAC1 activity causally leads to gene silencing, a differentiation block and oncogenic transformation.
- (v) HDAC1 gene knock-out in mice showed that HDAC1 has a profound function in embryonal stem cell proliferation by repressing cyclin-dependent kinase inhibitors p21<sup>waf1</sup> and p27<sup>kip1</sup> (Laguer et al. *Embo J.* 21, 2672-2681, 2002). Since p21<sup>waf1</sup> is induced by HDIs in many cancer cell lines, HDAC1 might be a crucial component in cancer cell proliferation as well. Initial siRNA based gene-knock down experiments in HeLa cells support this hypothesis (Glaser et al. 310, 529-536, 2003)
- (vi) HDAC2 is overexpressed in colon carcinoma upon constitutive activation of the wnt / $\beta$ -catenin/TCF signalling pathway by loss of functional adenomatosis polyposis coli (APC) protein as reported by Zhu et al. recently (*Cancer Cell* 5, 455-463, 2004)

On the molecular level, a plethora of published data with various HDAC inhibitors like Trichostatin A (TSA) showed that many cancer relevant genes are up- or down regulated. These include p21<sup>waf1</sup>, Cyclin E, transforming growth factor  $\beta$  (TGF $\beta$ ), p53 or the von Hippel-Lindau (VHL) tumor suppressor genes, which are upregulated, whereas Bcl-XL, bcl2, hypoxia inducible factor (HIF)1 $\alpha$ , vascular endothelial growth factor (VEGF) and cyclin A/D are down-regulated by HDAC inhibition (reviewed by Kramer et al. *Trends Endocrin Metabol* 12, 294-300, 2001). HDAC inhibitors arrest cells at G1 and G2/M within the cell cycle and deplete S-phase cells, as shown for Depsipeptide as an example (Sandor et al., *British J Cancer* 83, 817-825, 2000). HDAC inhibitory compounds induce p53 and caspase3/8 independent apoptosis and have broad anti-tumor activity. Anti-angiogenic activity was

described also, which might be related to down-regulation of VEGF and HIF1 $\alpha$ . In summary, HDAC inhibition effects tumor cells at different molecular levels and multiple cellular proteins are targeted.

Interestingly, HDAC inhibitors were found to induce cellular differentiation and this pharmacological activity might contribute to their anti-cancer activity as well. For example it was shown recently that suberoylanilide hydroxamic acid (SAHA) induces differentiation of breast cancer cell lines, exemplified by resynthesis of milk fat membrane globule protein (MFMG), milk fat globule protein and lipid (Munster et al. Cancer Res. 61, 8492, 2001).

There is growing rationale for synergism of HDAC inhibitors with chemotherapeutic as well as target specific cancer drugs. For example, synergism was shown for SAHA with the kinase / cdk inhibitor flavopiridol (Alemenara et al. Leukemia 16, 1331-1343, 2002), for LAQ-824 with the bcr-abl kinase inhibitor Glivec in CML cells (Nimmanapalli et al. Cancer Res. 63, 5126-5135, 2003) and for SAHA and Trichostatin A (TSA) with etoposide (VP16), cisplatin and doxorubicin (Kim et al. Cancer Res. 63, 7291-7300, 2003) and LBH589 with the hsp90 inhibitor 17-allyl-amino-demethoxy-geldanamycin (17-AAG; George et al. Blood online, Oct.28, 2004). Also it was shown that HDAC inhibition causes reexpression of estrogen or androgen receptors in breast and prostate cancer cells with the potential to resensitize these tumors to anti-hormone therapy (Yang et al. Cancer Res. 60, 6890-6894, 2000; Nakayama et al. Lab Invest 80, 1789-1796, 2000).

HDAC inhibitors from various chemical classes were described in the literature with four most important classes, namely (i) hydroxamic acid analogs, (ii) benzamide analogs, (iii) cyclic peptides / peptolides and (iv) fatty acid analogs. A comprehensive summary of known HDAC inhibitors was published recently (Miller et al. J Med Chem 46, 5097-5116, 2003). There is only limited data published regarding specificity of these histone deacetylase inhibitors. In general most hydroxamate based HDI are not specific regarding class I and II HDAC enzymes. For example. TSA inhibits HDACs 1, 3, 4, 6 and 10 with IC<sub>50</sub> values around 20nM, whereas HDAC8 was inhibited with IC<sub>50</sub> = 0.49  $\mu$ M (Tatamiya et al, AACR Annual Meeting 2004, Abstract #2451). But there are exceptions like the experimental HDI Tubacin, selective for the class II enzyme HDAC 6 (Haggarty et al. Proc natl Acad Sci USA 100, 4389-4394, 2003). In addition, data on class I selectivity of benzamide HDIs are emerging. MS-275 inhibited class I HDAC1 and 3 with IC<sub>50</sub> = 0.51  $\mu$ M and 1.7 $\mu$ M, respectively. In contrast class II HDACs 4, 6, 8 and 10 were inhibited with IC<sub>50</sub> values of >100 $\mu$ M, >100 $\mu$ M, 82.5 $\mu$ M and 94.7 $\mu$ M, respectively (Tatamiya et al, AACR Annual Meeting 2004, Abstract #2451). So far it is not clear if specificity towards HDAC class I or II enzymes or a defined single isoenzyme should be superior regarding therapeutic efficacy and index.

Clinical studies in cancer with HDAC inhibitors are on-going, namely with SAHA (Merck Inc.), Valproic acid, FK228 / Depsipeptide (Gloucester Pharmaceuticals / NCI), MS275 (Berlex-Schering), NVP LBH-589 (Novartis), PXD-101 (Topotarget / Curagen), MGCD0103 (methylgene Inc.) and Pivaloyloxymethylbutyrate / Pivanex (Titan Pharmaceuticals). These studies showed first evidence of

clinical efficacy, highlighted recently by partial and complete responses with FK228 / Depsipeptide in patients with peripheral T-cell lymphoma (Plekarz et al. Blood, 98, 2865-2868, 2001) and diffuse large B-cell lymphoma by SAHA (Kelly et al. J. Clin. Oncol. 23, 3923-3931, 2005).

Recent publications also showed possible medical use of HDAC inhibitors in disease different to cancer. These diseases include systemic lupus erythematosus (Mishra et al. J Clin Invest 111, 539-552, 2003; Reilly et al. J. Immunol. 173, 4171-4178, 2004), rheumatoid arthritis (Chung et al. Mol Therapy 8, 707-717, 2003; Nishida et al. Arthritis & Rheumatology 50, 3365-3376, 2004), inflammatory diseases (Leoni et al. Proc Natl Acad Sci USA 99, 2995-3000, 2002) and neurodegenerative diseases like Huntington's disease (Steffan et al. Nature 413, 739-743, 2001, Hockly et al. Proc Natl Acad Sci USA 100(4):2041-6, 2003).

Cancer chemotherapy was established based on the concept that cancer cells with uncontrolled proliferation and a high proportion of cells in mitosis are killed preferentially. Standard cancer chemotherapeutic drugs finally kill cancer cells upon induction of programmed cell death ("apoptosis") by targeting basic cellular processes and molecules, namely RNA/DNA (alkylating and carbamylating agents, platin analogs and topoisomerase inhibitors), metabolism (drugs of this class are named anti-metabolites) as well as the mitotic spindle apparatus (stabilizing and destabilizing tubulin inhibitors). Inhibitors of histone deacetylases (HDIs) constitute a new class of anti cancer drugs with differentiation and apoptosis inducing activity. By targeting histone deacetylases, HDIs effect histone (protein) acetylation and chromatin structure, inducing a complex transcriptional reprogramming, exemplified by reactivation of tumor suppressor genes and repression of oncogenes. Beside effecting acetylation of N-terminal lysine residues in core histone proteins, non-histone targets important for cancer cell biology like heat-shock-protein 90 (Hsp90) or the p53 tumor suppressor protein exist. The medical use of HDIs might not be restricted to cancer therapy, since efficacy in models for inflammatory diseases, rheumatoid arthritis and neurodegeneration was shown.

Benzoyl or acetyl substituted pyrrolyl propenamides are described in the public literature as HDAC-inhibitors, whereas the connectivity of the acyl-group is at position 2 or 3 of the pyrrole scaffold. (Mai et.al., Journal Med.Chem. 2004, Vol. 47, No. 5, 1098-1109; or Ragno et al., Journal Med. Chem. 2004, Vol. 47, No. 5, 1351-1359). Further pyrrolyl substituted hydroxamic acid derivatives are described in US4960787 as lipoxxygenase inhibitors or in US6432999 as cyclooxygenase inhibitors or in EP570594 as inhibitors of cell growth.

Various compounds, which are said to be HDAC inhibitors, are reported in WO 01/38322; WO 03/024448; US 2005/0234033; Journal Med. Chem. 2003, Vol. 46, No. 24, 5097-5116; Journal Med. Chem. 2003, Vol. 46, No. 4, 512-524; Journal Med. Chem. 2003, Vol. 46, No. 5, 820-830; and in Current Opinion Drug Discovery 2002, Vol. 5, 487-499.

N-Sulphonylpyrrole derivatives are described as HDAC inhibitors in the international application WO 2005/087724, the disclosure of which is incorporated herein by reference.

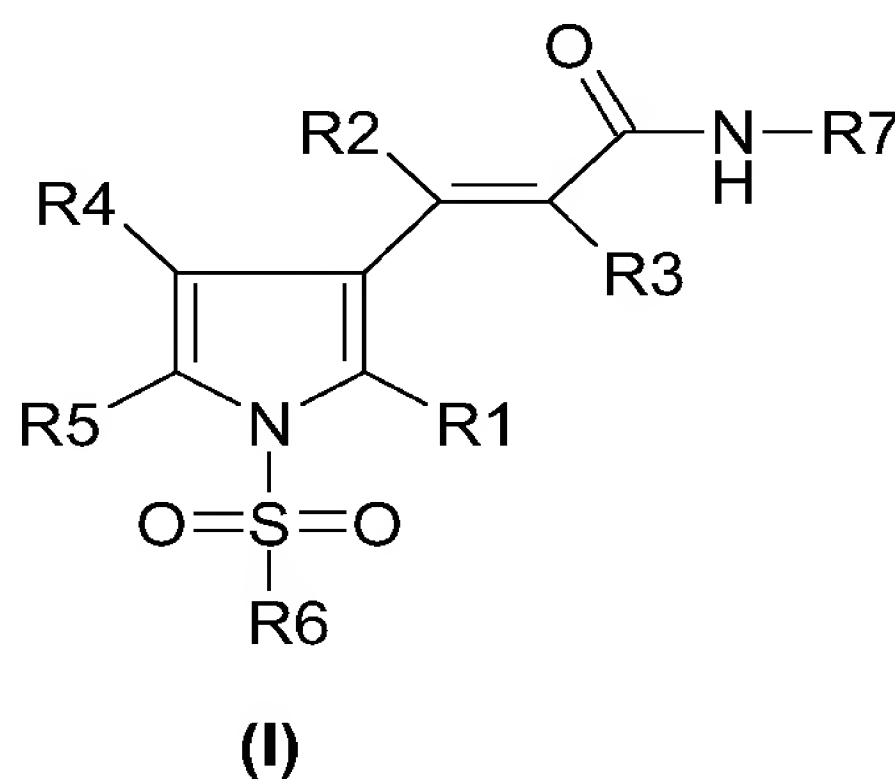
There remains a need in the art for new, well tolerated and more efficacious inhibitors of HDACs.

### **Description of the invention**

It has now been found that the N-sulphonylpyrrole derivatives, which are described in greater details below, differ profoundly from prior art compounds and are effective inhibitors of histone deacetylases and have surprising and particularly advantageous properties.

In addition and based on the foregoing, it has also been found, that certain salts of those N-sulphonylpyrrole derivatives have surprising and particularly advantageous properties, e.g. being crystalline materials which possess useful properties.

The invention thus relates, in a first aspect (aspect 1), to compounds of formula I



in which

R1 is hydrogen, 1-4C-alkyl, halogen, or 1-4C-alkoxy,

R2 is hydrogen or 1-4C-alkyl,

R3 is hydrogen or 1-4C-alkyl,

R4 is hydrogen, 1-4C-alkyl, halogen, or 1-4C-alkoxy,

R5 is hydrogen, 1-4C-alkyl, halogen, or 1-4C-alkoxy,

R6 is -T1-Q1, in which

T1 is a bond, or 1-4C-alkylene,

Q1 is Ar1, Aa1, Hh1, or Ah1, in which

Ar1 is phenyl, or R61- and/or R62-substituted phenyl, in which

R61 is 1-4C-alkyl, or -T2-N(R611)R612, in which

either

T2 is a bond, and

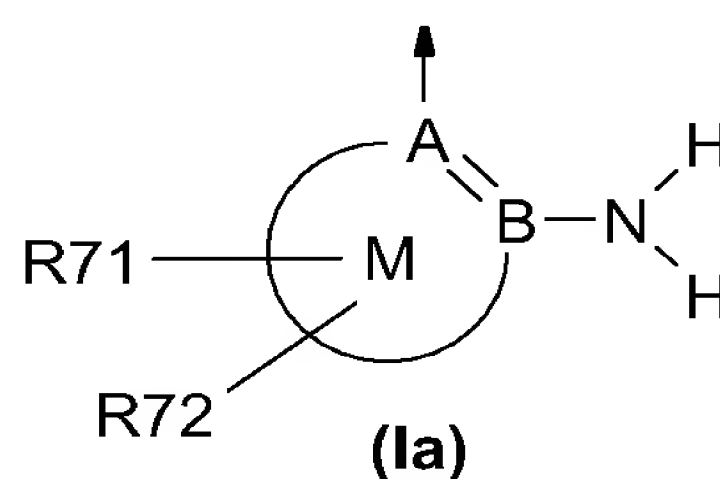


- R611 is hydrogen, 1-4C-alkyl, hydroxy-2-4C-alkyl, 1-4C-alkoxy-2-4C-alkyl, phenyl-1-4C-alkyl, or Har1-1-4C-alkyl, in which
- Har1 is optionally substituted by R6111 and/or R6112, and is a monocyclic or fused bicyclic 5- to 10-membered unsaturated heteroaromatic ring comprising one to three heteroatoms, each of which is selected from the group consisting of nitrogen, oxygen and sulfur, in which
- R6111 is halogen, or 1-4C-alkyl,
- R6112 is 1-4C-alkyl, and
- R612 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy-2-4C-alkyl or hydroxy-2-4C-alkyl, or R611 and R612 together and with inclusion of the nitrogen atom, to which they are bonded, form a heterocyclic ring Het1, in which
- Het1 is morpholino, thiomorpholino, S-oxo-thiomorpholino, S,S-dioxo-thiomorpholino, piperidino, pyrrolidino, piperazino, or 4N-(1-4C-alkyl)-piperazino,
- or
- T2 is 1-4C-alkylene, or 2-4C-alkylene interrupted by oxygen, and
- R611 is hydrogen, 1-4C-alkyl, hydroxy-2-4C-alkyl, 1-4C-alkoxy-2-4C-alkyl, phenyl-1-4C-alkyl, or Har1-1-4C-alkyl, in which
- Har1 is optionally substituted by R6111 and/or R6112, and is a monocyclic or fused bicyclic 5- to 10-membered unsaturated heteroaromatic ring comprising one to three heteroatoms, each of which is selected from the group consisting of nitrogen, oxygen and sulfur, in which
- R6111 is halogen, or 1-4C-alkyl,
- R6112 is 1-4C-alkyl, and
- R612 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy-2-4C-alkyl or hydroxy-2-4C-alkyl, or R611 and R612 together and with inclusion of the nitrogen atom, to which they are bonded, form a heterocyclic ring Het1, in which
- Het1 is morpholino, thiomorpholino, S-oxo-thiomorpholino, S,S-dioxo-thiomorpholino, piperidino, pyrrolidino, piperazino, 4N-(1-4C-alkyl)-piperazino, imidazolo, pyrrolo or pyrazolo,
- R62 is 1-4C-alkyl, 1-4C-alkoxy, halogen, cyano, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkylcarbonylamino, or 1-4C-alkylsulphonylamino,
- Aa1 is a bisaryl radical made up of two aryl groups, which are selected independently from a group consisting of phenyl and naphthyl, and which are linked together via a single bond,
- Hh1 is a bisheteroaryl radical made up of two heteroaryl groups, which are selected independently from a group consisting of monocyclic 5- or 6-membered heteroaryl radicals comprising one or two heteroatoms, each of which is selected from the group consisting of nitrogen, oxygen and sulfur, and which are linked together via a single bond,

Ah1 is a heteroaryl-aryl radical or an aryl-heteroaryl radical made up of a heteroaryl group selected from a group consisting of monocyclic 5- or 6-membered heteroaryl radicals comprising one or two heteroatoms, each of which is selected from the group consisting of nitrogen, oxygen and sulfur, and an aryl group selected from a group consisting of phenyl and naphthyl, whereby said heteroaryl and aryl groups are linked together via a single bond,

R7 is hydroxyl, or Cyc1, in which

Cyc1 is a ring system of formula Ia



in which

A is C (carbon),

B is C (carbon),

R71 is hydrogen, halogen, 1-4C-alkyl, or 1-4C-alkoxy,

R72 is hydrogen, halogen, 1-4C-alkyl, or 1-4C-alkoxy,

M with inclusion of A and B is either a ring Ar2 or a ring Har2, in which

Ar2 is a benzene ring,

Har2 is a monocyclic 5- or 6-membered unsaturated heteroaromatic ring comprising one to three heteroatoms, each of which is selected from the group consisting of nitrogen, oxygen and sulfur,

and the salts of these compounds.

The invention relates, in a second aspect (aspect 2), to compounds of formula I

in which

R1 is hydrogen, 1-4C-alkyl, halogen, or 1-4C-alkoxy,

R2 is hydrogen or 1-4C-alkyl,

R3 is hydrogen or 1-4C-alkyl,

R4 is hydrogen, 1-4C-alkyl, halogen, or 1-4C-alkoxy,

R5 is hydrogen, 1-4C-alkyl, halogen, or 1-4C-alkoxy,

R6 is -T1-Q1, in which

T1 is a bond, or 1-4C-alkylene,

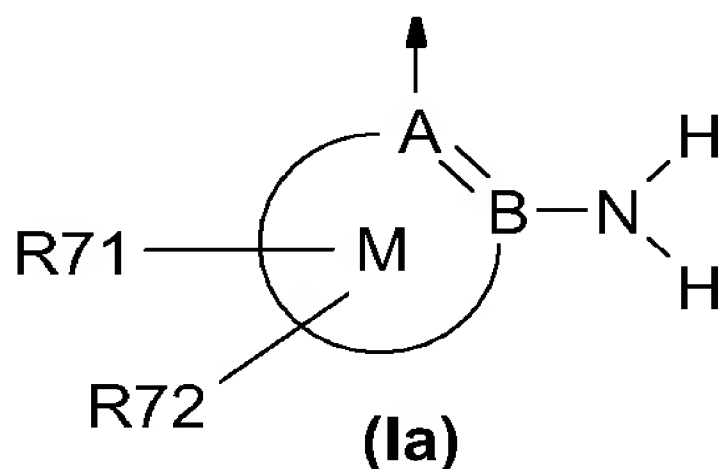
Q1 is Ar1, Aa1, Hh1, or Ah1, in which

Ar1 is phenyl, or R61- and/or R62-substituted phenyl, in which

R61 is 1-4C-alkyl, or -T2-N(R611)R612, in which



- T2 is a bond, 1-4C-alkylene, or 2-4C-alkylene interrupted by oxygen,
- R611 is hydrogen, 1-4C-alkyl, hydroxy-2-4C-alkyl, 1-4C-alkoxy-2-4C-alkyl, phenyl-1-4C-alkyl, or Har1-1-4C-alkyl, in which
- Har1 is optionally substituted by R6111 and/or R6112, and is a monocyclic or fused bicyclic 5- to 10-membered unsaturated heteroaromatic ring comprising one to three heteroatoms, each of which is selected from the group consisting of nitrogen, oxygen and sulfur, in which
- R6111 is halogen, or 1-4C-alkyl,
- R6112 is 1-4C-alkyl,
- R612 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy-2-4C-alkyl or hydroxy-2-4C-alkyl,
- R62 is 1-4C-alkyl, 1-4C-alkoxy, halogen, cyano, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkylcarbonylamino, or 1-4C-alkylsulphonylamino,
- Aa1 is a bisaryl radical made up of two aryl groups, which are selected independently from a group consisting of phenyl and naphthyl, and which are linked together via a single bond,
- Hh1 is a bisheteroaryl radical made up of two heteroaryl groups, which are selected independently from a group consisting of monocyclic 5- or 6-membered heteroaryl radicals comprising one or two heteroatoms, each of which is selected from the group consisting of nitrogen, oxygen and sulfur, and which are linked together via a single bond,
- Ah1 is a heteroaryl-aryl radical or an aryl-heteroaryl radical made up of a heteroaryl group selected from a group consisting of monocyclic 5- or 6-membered heteroaryl radicals comprising one or two heteroatoms, each of which is selected from the group consisting of nitrogen, oxygen and sulfur, and an aryl group selected from a group consisting of phenyl and naphthyl, whereby said heteroaryl and aryl groups are linked together via a single bond,
- R7 is hydroxyl, or Cyc1, in which
- Cyc1 is a ring system of formula Ia



in which

A is C (carbon),

B is C (carbon),  
R71 is hydrogen, halogen, 1-4C-alkyl, or 1-4C-alkoxy,  
R72 is hydrogen, halogen, 1-4C-alkyl, or 1-4C-alkoxy,  
M with inclusion of A and B is either a ring Ar2 or a ring Har2, in which  
Ar2 is a benzene ring,  
Har2 is a monocyclic 5- or 6-membered unsaturated heteroaromatic ring comprising one to three heteroatoms, each of which is selected from the group consisting of nitrogen, oxygen and sulfur,  
and the salts of these compounds.

The invention relates, in a third aspect (aspect 3), to certain salts of the compounds of formula I with hydrochloric acid, and to crystalline forms thereof.

In more detail, aspect 3 of this invention refers to salts of a compound selected from  
(E)- (E)-N-hydroxy-3-(1-[4-(((2-(1H-indol-2-yl)-ethyl)-methyl-amino)-methyl)-benzene sulfonyl]-1H-pyrrol-3-yl)-acrylamide,  
(E)-3-[1-(4-dimethylaminomethyl-benzenesulfonyl)-1H-pyrrol-3-yl]-N-hydroxy-acrylamide, and  
(E)-N-hydroxy-3-[1-(5-pyridin-2-yl-thiophene-2-sulfonyl)-1H-pyrrol-3-yl]-acrylamide  
with hydrochloric acid,  
their hydrates and to crystalline forms of these salts and hydrates.

1-4C-Alkyl represents a straight-chain or branched alkyl radical having 1 to 4 carbon atoms. Examples which may be mentioned are the butyl, isobutyl, sec-butyl, tert-butyl, propyl, isopropyl and preferably the ethyl and methyl radicals.

2-4C-Alkyl represents a straight-chain or branched alkyl radical having 2 to 4 carbon atoms. Examples which may be mentioned are the butyl, isobutyl, sec-butyl, tert-butyl, propyl, isopropyl and preferably the ethyl and propyl radicals.

1-4C-Alkylene is a branched or, particularly, straight chain alkylene radical having 1 to 4 carbon atoms. Examples which may be mentioned are the methylene (-CH<sub>2</sub>-), ethylene (-CH<sub>2</sub>-CH<sub>2</sub>-), trimethylene (-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-) and the tetramethylene (-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-) radical.

2-4C-Alkylene interrupted by oxygen stands for a straight chain alkylene radical having 1 to 4 carbon atoms which is suitably interrupted by an oxygen atom such as, for example, the [-CH<sub>2</sub>-CH<sub>2</sub>-O-CH<sub>2</sub>-CH<sub>2</sub>-] radical.

1-4C-Alkoxy represents radicals which, in addition to the oxygen atom, contain a straight-chain or branched alkyl radical having 1 to 4 carbon atoms. Examples which may be mentioned are the butoxy,

isobutoxy, sec-butoxy, tert-butoxy, propoxy, isopropoxy and preferably the ethoxy and methoxy radicals.

1-4C-Alkoxy-1-4C-alkyl represents one of the abovementioned 1-4C-alkyl radicals, which is substituted by one of the abovementioned 1-4C-alkoxy radicals. Examples which may be mentioned are the methoxymethyl, the methoxyethyl and the isopropoxyethyl radicals, particularly the 2-methoxyethyl and the 2-isopropoxyethyl radicals.

1-4C-Alkoxy-2-4C-alkyl represents one of the abovementioned 2-4C-alkyl radicals, which is substituted by one of the abovementioned 1-4C-alkoxy radicals. Examples which may be mentioned are the methoxyethyl, ethoxyethyl and the isopropoxyethyl radicals, particularly the 2-methoxyethyl, the 2-ethoxyethyl and the 2-isopropoxyethyl radicals.

Hydroxy-2-4C-alkyl represents one of the abovementioned 2-4C-alkyl radicals, which is substituted by a hydroxy radical. An example which may be mentioned is the 2-hydroxyethyl or the 3-hydroxypropyl radical.

Phenyl-1-4C-alkyl stands for one of the abovementioned 1-4C-alkyl radicals, which is substituted by a phenyl radical. Examples which may be mentioned are the benzyl and the phenethyl radicals.

Halogen within the meaning of the invention is bromine or, in particular, chlorine or fluorine.

1-4C-Alkylcarbonyl represents a radical which, in addition to the carbonyl group, contains one of the abovementioned 1-4C-alkyl radicals. An example which may be mentioned is the acetyl radical.

1-4C-Alkylcarbonylamino represents an amino radical which is substituted by one of the abovementioned 1-4C-alkylcarbonyl radicals. An example which may be mentioned is the acetamido radical  $[\text{CH}_3\text{C}(\text{O})\text{-NH-}]$ .

1-4C-Alkylsulphonylamino is, for example, the propylsulfonylamino  $[\text{C}_3\text{H}_7\text{S}(\text{O})_2\text{NH-}]$ , the ethylsulfonylamino  $[\text{C}_2\text{H}_5\text{S}(\text{O})_2\text{NH-}]$  and the methylsulfonylamino  $[\text{CH}_3\text{S}(\text{O})_2\text{NH-}]$  radical.

Aa1 is a bisaryl radical made up of two aryl groups, which are selected independently from a group consisting of phenyl and naphthyl, and which are linked together via a single bond.

Aa1 may include, without being restricted thereto, the biphenyl radical, e.g. the 1,1'-biphen-4-yl or 1,1'-biphen-3-yl radical.

Hh1 is a bisheteroaryl radical made up of two heteroaryl groups, which are selected independently from a group consisting of monocyclic 5- or 6-membered heteroaryl

radicals comprising one or two heteroatoms, each of which is selected from the group consisting of nitrogen, oxygen and sulfur, and which are linked together via a single bond.

Hh1 may include, without being restricted thereto, the bithiophenyl, bipyridyl, pyrazolyl-pyridinyl (particularly pyrazol-1-yl-pyridinyl), imidazolyl-pyridinyl (particularly imidazol-1-yl-pyridinyl) or the pyridinyl-thiophenyl radical, e.g. the 5-(pyridin-2-yl)-thiophen-2-yl radical.

In a special detail, exemplary Hh1 radicals may include pyridinyl-thiophenyl, e.g. 5-(pyridin-2-yl)-thiophen-2-yl.

Ah1 is a heteroarylaryl radical or an arylheteroaryl radical made up of a heteroaryl group selected from a group consisting of monocyclic 5- or 6-membered heteroaryl radicals comprising one or two heteroatoms, each of which is selected from the group consisting of nitrogen, oxygen and sulfur, and an aryl group selected from a group consisting of phenyl and naphthyl, whereby said heteroaryl and aryl groups are linked together via a single bond.

The Ah1 radical can be bonded either via said heteroaryl or via said aryl moiety to the parent molecular group.

A particular embodiment of said Ah1 radicals refers to heteroaryl-phenyl radicals, e.g. 3-(heteroaryl)-phenyl or 4-(heteroaryl)-phenyl radicals.

Ah1 may include, without being restricted thereto, the phenyl-thiophenyl or phenyl-pyridyl radicals.

Alternatively, Ah1 may include, without being restricted thereto the furanyl-phenyl, pyrazolyl-phenyl (e.g. pyrazol-1-yl-phenyl or 1H-pyrazol-4-yl-phenyl), imidazolyl-phenyl (e.g. imidazol-1-yl-phenyl) or pyridinyl-phenyl radicals.

In a special detail, exemplary Ah1 radicals may include 3-(pyrazolyl)-phenyl, 4-(pyrazolyl)-phenyl, 4-(pyridinyl)-phenyl or 3-(pyridinyl)-phenyl.

In a further special detail, exemplary Ah1 radicals may include 3-(pyrazol-1-yl)-phenyl, 4-(pyrazol-1-yl)-phenyl, 4-(pyridin-4-yl)-phenyl, 3-(pyridin-4-yl)-phenyl, 4-(pyridin-3-yl)-phenyl, 3-(pyridin-3-yl)-phenyl, 3-(1H-pyrazol-4-yl)-phenyl or 4-(1H-pyrazol-4-yl)-phenyl.

It is to be stated, that each of the radicals Hh1 and Ah1 is bonded preferably via a ring carbon atom to the moiety T1.

Har1 is optionally substituted by R6111 and/or R6112, and is a monocyclic or fused bicyclic 5- to 10-membered unsaturated (heteroaromatic) heteroaryl radical comprising one to three heteroatoms, each of which is selected from the group consisting of nitrogen, oxygen and sulfur. In one detail, fused, in

particular benzo-fused, bicyclic 9- or 10-membered heteroaryl radicals comprising one to three, in particular one or two, heteroatoms, each of which is selected from the group consisting of nitrogen, oxygen and sulfur, are to be mentioned. Examples of Har1 include, without being restricted thereto, thiophenyl, furanyl, pyrrolyl, oxazolyl, isoxazolyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl; and, in particular, the stable benzo-fused derivatives thereof, such as e.g. benzothiophenyl, benzofuranyl, indolyl, benzoxazolyl, benzothiazolyl, indazolyl, benzimidazolyl, benzisoxazolyl, benzisothiazolyl, benzofurazanyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, phthalazinyl or cinnolinyl; and purinyl, indolizinyl, naphthyridinyl or pteridinyl.

In a special detail, exemplary Har1 radicals may include pyridinyl, benzimidazolyl, benzoxazolyl, benzofuranyl, benzothiophenyl and indolyl, such as e.g. pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, benzimidazol-2-yl, benzoxazol-2-yl, benzofuran-2-yl, benzofuran-3-yl, benzothiophen-2-yl, benzothiophen-3-yl, indol-2-yl, indol-3-yl or indol-5-yl.

In a further special detail, an exemplary Har1 radical may be indolyl, such as e.g. indol-2-yl, indol-3-yl or indol-5-yl.

Yet in a further special detail, an exemplary Har1 radical may be pyridinyl, such as e.g. pyridin-2-yl, pyridin-3-yl or pyridin-4-yl.

As further examples of Har1, the R6111- and/or R6112-substituted derivatives of the abovementioned exemplary Har1 radicals may be mentioned.

Har1-1-4C-alkyl stands for one of the abovementioned 1-4C-alkyl radicals, such as e.g. methyl, ethyl or propyl, substituted by one of the abovementioned Har1 radicals, such as e.g. imidazolyl, benzimidazolyl, indolyl or pyrrolyl and the like or the substituted derivatives thereof. As examples may be mentioned, without being restricted thereto, pyridinylmethyl (e.g. pyridin-3-yl-methyl), imidazolylmethyl, pyrrolylmethyl, 2-imidazolylethyl (e.g. 2-imidazol-5-yl-ethyl), 2-pyridinylethyl, 3-(benzofuran-2-yl)propyl, 3-(benzimidazol-2-yl)propyl, 2-indolylethyl (e.g. 2-indol-2-yl-ethyl or 2-indol-3-yl-ethyl), indolylmethyl (e.g. indol-2-yl-methyl, indol-3-yl-methyl or indol-5-yl-methyl), 2-benzimidazolylethyl (e.g. 2-benzimidazol-2-ylethyl), benzimidazolylmethyl (e.g. benzimidazol-2-yl-methyl), and the like.

In a special detail, exemplary Har1-1-4C-alkyl radicals may include pyridinylmethyl (e.g. pyridin-3-yl-methyl, pyridin-4-yl-methyl or pyridin-4-yl-methyl), 2-pyridinylethyl (e.g. 2-pyridin-3-yl-ethyl), indolylmethyl (e.g. indol-2-yl-methyl, indol-3-yl-methyl or indol-5-yl-methyl) or 2-indolylethyl (e.g. 2-indolyl-2-yl-ethyl or 2-indolyl-3-yl-ethyl).

In a further special detail, exemplary Har1-1-4C-alkyl radicals may include pyridin-3-yl-methyl, pyridin-4-yl-methyl, 2-pyridin-3-yl-ethyl, indol-2-yl-methyl, indol-3-yl-methyl, indol-5-yl-methyl, 2-indolyl-2-yl-ethyl or 2-indolyl-3-yl-ethyl.

In the context of the radical Har1-1-4C-alkyl, it is to be stated, that the portion Har1 is bonded preferably via a ring carbon atom to the 1-4C-alkyl moiety.

One embodiment of those Har1-1-4C-alkyl radicals, in which the Har1 moiety is a fused bicyclic ring containing a benzene ring, refers to those radicals, in which the Har1 moiety is preferably bonded to the 1-4C-alkyl moiety via a carbon ring atom of the ring comprising one or more heteroatoms.

Another embodiment of those Har1-1-4C-alkyl radicals, in which the Har1 moiety is a fused bicyclic ring containing a benzene ring, refers to those radicals, in which the Har1 moiety is preferably bonded to the 1-4C-alkyl moiety via a carbon ring atom of the benzene ring.

Har2 stands for a monocyclic 5- or 6-membered unsaturated heteroaromatic ring comprising one to three heteroatoms, each of which is selected from the group consisting of nitrogen, oxygen and sulfur. Har2 may include, without being restricted thereto, thiophene, oxazole, isoxazole, thiazole, isothiazole, imidazole, pyrazole, triazole, thiadiazole, oxadiazole, pyridine, pyrimidine, pyrazine or pyridazine.

In a special detail, an exemplary Har2 radical may be pyridine.

Cyc1 stands for a ring system of formula Ia, which is bonded to the nitrogen atom of the carboxamide group via the moiety A. Cyc1 may include, without being restricted thereto, 2-aminophenyl substituted by R71 and/or R72.

Naphthyl, alone or as part of another group, includes naphthalen-1-yl and naphthalen-2-yl.

In the meaning of the present invention, it is to be understood, that, when two structural portions of the compounds according to this invention are linked via a constituent which has the meaning "bond", then said two portions are directly attached to another via a single bond.

In general, unless otherwise mentioned the heterocyclic groups mentioned herein refer to all of the possible isomeric forms thereof.

The heterocyclic groups mentioned herein refer, unless otherwise noted, in particular to all of the possible positional isomers thereof.

Thus, for example, the term pyridyl or pyridinyl, alone or as part of another group, includes pyridin-2-yl, pyridin-3-yl and pyridin-4-yl.

Constituents which are optionally substituted as stated herein, may be substituted, unless otherwise noted, at any possible position.

The carbocyclic groups, alone or as part of other groups, mentioned herein may be substituted by their given substituents or parent molecular groups, unless otherwise noted, at any substitutable ring carbon atom.

The heterocyclic groups, alone or as part of other groups, mentioned herein may be substituted by their given substituents or parent molecular groups, unless otherwise noted, at any possible position, such as e.g. at any substitutable ring carbon or ring nitrogen atom.

Rings containing quaternizable imino-type ring nitrogen atoms ( $-N=$ ) may be preferably not quaternized on these imino-type ring nitrogen atoms by the mentioned substituents or parent molecular groups.

Any heteroatom of a heterocyclic ring with unsatisfied valences mentioned herein is assumed to have the hydrogen atom(s) to satisfy the valences.

When any variable occurs more than one time in any constituent, each definition is independent.

Suitable salts for compounds of the formula I - depending on substitution - are all acid addition salts or all salts with bases. Particular mention may be made of the pharmacologically tolerable inorganic and organic acids and bases customarily used in pharmacy. Those suitable are, on the one hand, water-insoluble and, particularly, water-soluble acid addition salts with acids such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, sulphuric acid, acetic acid, citric acid, D-gluconic acid, benzoic acid, 2-(4-hydroxybenzoyl)benzoic acid, butyric acid, sulphosalicylic acid, maleic acid, lauric acid, malic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, embonic acid, stearic acid, toluenesulphonic acid, methanesulphonic acid or 3-hydroxy-2-naphthoic acid, the acids being employed in salt preparation - depending on whether a mono- or polybasic acid is concerned and depending on which salt is desired - in an equimolar quantitative ratio or one differing therefrom.

On the other hand, salts with bases are - depending on substitution - also suitable. As examples of salts with bases are mentioned the lithium, sodium, potassium, calcium, aluminium, magnesium, titanium, ammonium, meglumine or guanidinium salts, here, too, the bases being employed in salt preparation in an equimolar quantitative ratio or one differing therefrom.

Salts which are unsuitable for pharmaceutical uses but which can be employed, for example, for the isolation, purification or preparation of free compounds of formula I or their pharmaceutically acceptable salts, are also included.



Pharmacologically intolerable salts, which can be obtained, for example, as process products during the preparation of the compounds according to the invention on an industrial scale, are converted into pharmacologically tolerable salts by processes known to the person skilled in the art.

According to expert's knowledge the compounds of formula I of the invention as well as their salts may contain, e.g. when isolated in crystalline form, varying amounts of solvents. Included within the scope of the invention are therefore all solvates and in particular all hydrates of the compounds of formula I as well as all solvates and in particular all hydrates of the salts of the compounds of formula I.

In one embodiment of this invention, salts of the compounds of formula I include salts of compounds of formula I with hydrochloric acid.

Furthermore, the invention includes all conceivable polymorphic forms of the compounds of the present invention in pure form as well as any mixtures thereof.

The substituents R61 and R62 of compounds of formula I can be attached in the ortho, meta or para position with respect to the binding position in which the phenyl ring is bonded to T1, whereby preference is given to the attachment in the meta or, particularly, in the para position.

In another embodiment, Ar1 is phenyl which is mono-substituted by R61, whereby preference is given to the attachment of R61 in the meta or para position with respect to the binding position in which the phenyl ring is bonded to T1.

In yet another embodiment, Ar1 is phenyl which is mono-substituted by R61, whereby preference is given to the attachment of R61 in the para position with respect to the binding position in which the phenyl ring is bonded to T1.

In still yet another embodiment, Ar1 is phenyl which is mono-substituted by R61, whereby preference is given to the attachment of R61 in the meta position with respect to the binding position in which the phenyl ring is bonded to T1.

Compounds according to aspect 1 of the present invention more worthy to be mentioned are those compounds of formula I

in which

- R1 is hydrogen, or 1-4C-alkyl,
- R2 is hydrogen, or 1-4C-alkyl,
- R3 is hydrogen, or 1-4C-alkyl,
- R4 is hydrogen, or 1-4C-alkyl,
- R5 is hydrogen, or 1-4C-alkyl,
- R6 is -T1-Q1, in which
- T1 is a bond, or 1-4C-alkylene,
- Q1 is Ar1, Aa1, Hh1, or Ah1, in which
- Ar1 is phenyl, or R61-substituted phenyl, in which

R61 is 1-4C-alkyl, or -T2-N(R611)R612, in which  
either  
T2 is a bond,  
R611 is hydrogen, 1-4C-alkyl, phenyl-1-4C-alkyl, or Har1-1-4C-alkyl, in which  
Har1 is either  
a monocyclic 5-membered unsaturated heteroaromatic ring comprising one, two or three  
heteroatoms, each of which is selected from the group consisting of nitrogen, oxygen and  
sulfur, or  
a monocyclic 6-membered unsaturated heteroaromatic ring comprising one or two nitrogen  
atoms, or  
a fused bicyclic 9-membered unsaturated heteroaromatic ring comprising one, two or three  
heteroatoms, each of which is selected from the group consisting of nitrogen, oxygen and  
sulfur, or  
a fused bicyclic 10-membered unsaturated heteroaromatic ring comprising one or two  
heteroatoms, each of which is selected from the group consisting of nitrogen, oxygen and  
sulfur, and  
R612 is hydrogen, 1-4C-alkyl, or hydroxy-2-4C-alkyl,  
or R611 and R612 together and with inclusion of the nitrogen atom, to which they are bonded, form a  
heterocyclic ring Het1, in which  
Het1 is morpholino,  
or  
T2 is 1-4C-alkylene,  
R611 is hydrogen, 1-4C-alkyl, phenyl-1-4C-alkyl, or Har1-1-4C-alkyl, in which  
Har1 is either  
a monocyclic 5-membered unsaturated heteroaromatic ring comprising one, two or three  
heteroatoms, each of which is selected from the group consisting of nitrogen, oxygen and  
sulfur, or  
a monocyclic 6-membered unsaturated heteroaromatic ring comprising one or two nitrogen  
atoms, or  
a fused bicyclic 9-membered unsaturated heteroaromatic ring comprising one, two or three  
heteroatoms, each of which is selected from the group consisting of nitrogen, oxygen and  
sulfur, or  
a fused bicyclic 10-membered unsaturated heteroaromatic ring comprising one or two  
heteroatoms, each of which is selected from the group consisting of nitrogen, oxygen and  
sulfur, and  
R612 is hydrogen, 1-4C-alkyl, or hydroxy-2-4C-alkyl,  
or R611 and R612 together and with inclusion of the nitrogen atom, to which they are bonded, form a  
heterocyclic ring Het1, in which  
Het1 is morpholino,  
Aa1 is a biphenyl radical,

- 17 -

Hh1 is a bipyridyl, pyrazolyl-pyridinyl, imidazolyl-pyridinyl, or pyridinyl-thiophenyl radical,  
Ah1 is a pyridinyl-phenyl, pyrazolyl-phenyl, or imidazolyl-phenyl radical,  
R7 is hydroxyl, or 2-aminophenyl,  
and the salts of these compounds.

Compounds according to aspect 2 of the present invention more worthy to be mentioned are those compounds of formula I

in which

R1 is hydrogen, or 1-4C-alkyl,  
R2 is hydrogen, or 1-4C-alkyl,  
R3 is hydrogen, or 1-4C-alkyl,  
R4 is hydrogen, or 1-4C-alkyl,  
R5 is hydrogen, or 1-4C-alkyl,  
R6 is -T1-Q1, in which  
T1 is a bond, or 1-4C-alkylene,  
Q1 is Ar1, or Aa1, in which  
Ar1 is phenyl, or R61-substituted phenyl, in which  
R61 is 1-4C-alkyl, or -T2-N(R611)R612, in which  
T2 is a bond, or 1-4C-alkylene,  
R611 is hydrogen, 1-4C-alkyl, or Har1-1-4C-alkyl, in which  
Har1 is imidazolyl, benzimidazolyl, indolyl or pyrrolyl,  
R612 is hydrogen, or 1-4C-alkyl,  
Aa1 is a biphenyl radical,  
R7 is hydroxyl, or 2-aminophenyl,  
and the salts of these compounds.

Compounds according to aspect 1 of the present invention in particular worthy to be mentioned are those compounds of formula I

in which

R1 is hydrogen,  
R2 is hydrogen,  
R3 is hydrogen,  
R4 is hydrogen,  
R5 is hydrogen,  
R6 is -T1-Q1, Aa1, Hh1, or Ah1, in which  
T1 is a bond, or 1-2C-alkylene,  
Q1 is Ar1, in which  
Ar1 is phenyl, or R61-substituted phenyl, in which  
R61 is 1-4C-alkyl, or -T2-N(R611)R612, in which  
either

T2 is a bond,  
 R611 is hydrogen, 1-4C-alkyl, phenyl-1-2C-alkyl, or Har1-1-2C-alkyl, in which  
 Har1 is pyridinyl, benzimidazolyl, benzoxazolyl, benzofuranyl, benzothiophenyl or indolyl, and  
 R612 is hydrogen, 1-4C-alkyl, or hydroxy-2-3C-alkyl,  
 or R611 and R612 together and with inclusion of the nitrogen atom, to which they are bonded, form a  
 heterocyclic ring Het1, in which  
 Het1 is morpholino,  
 or  
 T2 is 1-2C-alkylene,  
 R611 is hydrogen, 1-4C-alkyl, phenyl-1-2C-alkyl, or Har1-1-2C-alkyl, in which  
 Har1 is pyridinyl, benzimidazolyl, benzoxazolyl, benzofuranyl, benzothiophenyl or indolyl, and  
 R612 is hydrogen, 1-4C-alkyl, or hydroxy-2-3C-alkyl,  
 or R611 and R612 together and with inclusion of the nitrogen atom, to which they are bonded, form a  
 heterocyclic ring Het1, in which  
 Het1 is morpholino,  
 Aa1 is a biphenyl radical,  
 Hh1 is a bipyridyl, pyrazolyl-pyridinyl, imidazolyl-pyridinyl, or pyridinyl-thiophenyl radical,  
 Ah1 is a pyridinyl-phenyl, pyrazolyl-phenyl, or imidazolyl-phenyl radical,  
 R7 is hydroxyl, or 2-aminophenyl,  
 and the salts of these compounds.

Compounds according to aspect 2 of the present invention in particular worthy to be mentioned are those compounds of formula I

in which

R1 is hydrogen,  
 R2 is hydrogen,  
 R3 is hydrogen,  
 R4 is hydrogen,  
 R5 is hydrogen,  
 R6 is -T1-Q1, or biphenyl, in which  
 T1 is a bond, or 1-2C-alkylene,  
 Q1 is Ar1, in which  
 Ar1 is phenyl, or R61-substituted phenyl, in which  
 R61 is 1-4C-alkyl, or -T2-N(R611)R612, in which  
 T2 is a bond, or 1-2C-alkylene,  
 R611 is 1-4C-alkyl, or Har1-1-2C-alkyl, in which  
 Har1 is benzimidazolyl or indolyl,  
 R612 is 1-4C-alkyl,  
 R7 is hydroxyl, or 2-aminophenyl,  
 and the salts of these compounds.

Compounds according to aspect 1 of the present invention in more particular worthy to be mentioned are those compounds of formula I

in which

R1 is hydrogen,  
 R2 is hydrogen,  
 R3 is hydrogen,  
 R4 is hydrogen,  
 R5 is hydrogen,  
 R6 is -T1-Q1, Aa1, Hh1, Ah1, or benzyl, in which

T1 is a bond,

Q1 is Ar1, in which

Ar1 is phenyl, or R61-substituted phenyl, in which

R61 is 1-4C-alkyl, or -T2-N(R611)R612, in which

either

T2 is a bond,

R611 is 1-4C-alkyl, and

R612 is 1-4C-alkyl,

or

T2 is 1-2C-alkylene,

R611 is hydrogen, 1-4C-alkyl, phenyl-1-2C-alkyl, or Har1-1-2C-alkyl, in which

Har1 is pyridinyl, or indolyl, and

R612 is hydrogen, 1-4C-alkyl, or hydroxy-2-3C-alkyl,

or R611 and R612 together and with inclusion of the nitrogen atom, to which they are bonded, form a heterocyclic ring Het1, in which

Het1 is morpholino,

Aa1 is 1,1'-biphen-4-yl or 1,1'-biphen-3-yl,

Hh1 is a pyridinyl-thiophenyl radical,

Ah1 is a 3-(pyridinyl)-phenyl, 3-(pyrazolyl)-phenyl, 4-(pyridinyl)-phenyl or 4-(pyrazolyl)-phenyl radical,

R7 is hydroxyl, or 2-aminophenyl,

and the salts of these compounds.

Compounds according to aspect 2 of the present invention in more particular worthy to be mentioned are those compounds of formula I

in which

R1 is hydrogen,

R2 is hydrogen,

R3 is hydrogen,

R4 is hydrogen,

- 20 -

R5 is hydrogen,  
 R6 is -T1-Q1, biphenyl, or benzyl, in which  
 T1 is a bond,  
 Q1 is Ar1, in which  
 Ar1 is R61-substituted phenyl, in particular 4-(R61)-phenyl, in which  
 R61 is methyl, dimethylamino, or -T2-N(R611)R612, in which  
 T2 is methylene,  
 R611 is methyl or 2-(indol-2-yl)ethyl,  
 R612 is methyl,  
 R7 is hydroxyl, or 2-aminophenyl,  
 and the salts of these compounds.

Compounds according to aspect 1 of the present invention to be emphasized are those compounds of formula I

in which

R1 is hydrogen,  
 R2 is hydrogen,  
 R3 is hydrogen,  
 R4 is hydrogen,  
 R5 is hydrogen,  
 R6 is -T1-Q1, Aa1, Hh1, Ah1, or benzyl, in which  
 T1 is a bond,  
 Q1 is Ar1, in which  
 Ar1 is phenyl, 3-(R61)-phenyl, or 4-(R61)-phenyl, in which  
 R61 is methyl, or -T2-N(R611)R612, in which  
 either  
 T2 is a bond,  
 R611 is methyl, and  
 R612 is methyl,  
 or  
 T2 is methylene,  
 R611 is hydrogen, methyl, isobutyl, benzyl, Har1-methyl, or 2-(Har1)-ethyl in which  
 Har1 is pyridinyl or indolyl, and  
 R612 is hydrogen, methyl, or 2-hydroxy-ethyl,  
 or R611 and R612 together and with inclusion of the nitrogen atom, to which they are bonded, form a  
 heterocyclic ring Het1, in which  
 Het1 is morpholino,  
 Aa1 is 1,1'-biphen-4-yl or 1,1'-biphen-3-yl,  
 Hh1 is a pyridinyl-thiophenyl radical,

Ah1 is a 3-(pyridinyl)-phenyl, 3-(pyrazolyl)-phenyl, 4-(pyridinyl)-phenyl or 4-(pyrazolyl)-phenyl radical,

R7 is hydroxyl, or 2-aminophenyl,  
and the salts of these compounds.

Compounds according to aspect 1 of the present invention to be more emphasized are those compounds of formula I

in which

R1 is hydrogen,

R2 is hydrogen,

R3 is hydrogen,

R4 is hydrogen,

R5 is hydrogen,

R6 is -T1-Q1, Aa1, Hh1, Ah1, or benzyl, in which

T1 is a bond,

Q1 is Ar1, in which

Ar1 is phenyl, 3-(R61)-phenyl, or 4-(R61)-phenyl, in which

R61 is methyl, or -T2-N(R611)R612, in which

either

T2 is a bond,

R611 is methyl, and

R612 is methyl,

or

T2 is methylene,

R611 is hydrogen, methyl, isobutyl, benzyl, Har1-methyl, or 2-(Har1)-ethyl in which

Har1 is pyridin-3-yl, pyridin-4-yl, indol-2-yl, indol-3-yl or indol-5-yl, and

R612 is hydrogen, methyl, or 2-hydroxy-ethyl,

or R611 and R612 together and with inclusion of the nitrogen atom, to which they are bonded, form a heterocyclic ring Het1, in which

Het1 is morpholino,

Aa1 is 1,1'-biphen-4-yl or 1,1'-biphen-3-yl,

Hh1 is 5-(pyridin-2-yl)-thiophen-2-yl,

Ah1 is 3-(pyridin-3-yl)-phenyl, 3-(pyridin-4-yl)-phenyl, 3-(pyrazol-1-yl)-phenyl, 3-(1H-pyrazol-4-yl)-phenyl, 4-(pyridin-3-yl)-phenyl, 4-(pyridin-4-yl)-phenyl, 4-(pyrazol-1-yl)-phenyl or 4-(1H-pyrazol-4-yl)-phenyl,

R7 is hydroxyl, or 2-aminophenyl,

and the salts of these compounds.

Compounds according to aspect 1 of the present invention to be in particular emphasized are those compounds of formula I



in which

R1 is hydrogen,

R2 is hydrogen,

R3 is hydrogen,

R4 is hydrogen,

R5 is hydrogen,

R6 is -T1-Q1, Aa1, Hh1, Ah1, or benzyl, in which

T1 is a bond,

Q1 is Ar1, in which

Ar1 is phenyl, 3-(R61)-phenyl, or 4-(R61)-phenyl, in which

R61 is methyl, or -T2-N(R611)R612, in which

either

T2 is a bond,

R611 is methyl, and

R612 is methyl,

or

T2 is methylene,

R611 is hydrogen, isobutyl, benzyl, Har1-methyl, or 2-(Har1)-ethyl, in which

Har1 is pyridin-3-yl, pyridin-4-yl, indol-2-yl, indol-3-yl or indol-5-yl, and

R612 is hydrogen,

or

T2 is methylene,

R611 is methyl, or 2-(Har1)-ethyl, in which

Har1 is indol-2-yl, and

R612 is methyl,

or

T2 is methylene,

R611 is 2-(Har1)-ethyl, in which

Har1 is indol-2-yl, and

R612 is 2-hydroxy-ethyl,

or

T2 is methylene, and

R611 and R612 together and with inclusion of the nitrogen atom, to which they are bonded, form a heterocyclic ring Het1, in which

Het1 is morpholino,

Aa1 is 1,1'-biphen-4-yl or 1,1'-biphen-3-yl,

Hh1 is 5-(pyridin-2-yl)-thiophen-2-yl,

Ah1 is 3-(pyridin-3-yl)-phenyl, 3-(pyridin-4-yl)-phenyl, 3-(pyrazol-1-yl)-phenyl, 3-(1H-pyrazol-4-yl)-phenyl, 4-(pyridin-3-yl)-phenyl, 4-(pyridin-4-yl)-phenyl, 4-(pyrazol-1-yl)-phenyl or 4-(1H-pyrazol-4-yl)-phenyl,

R7 is hydroxyl,  
and the salts of these compounds.

Yet compounds according to aspect 1 of the present invention to be in particular emphasized are those compounds of formula I

in which

R1 is hydrogen,

R2 is hydrogen,

R3 is hydrogen,

R4 is hydrogen,

R5 is hydrogen,

R6 is -T1-Q1, Aa1, Hh1, Ah1, or benzyl, in which

T1 is a bond,

Q1 is Ar1, in which

Ar1 is phenyl, 3-(R61)-phenyl, or 4-(R61)-phenyl, in which

R61 is methyl, or -T2-N(R611)R612, in which

either

T2 is a bond,

R611 is methyl, and

R612 is methyl,

or

T2 is methylene,

R611 is hydrogen, isobutyl, benzyl, Har1-methyl, or 2-(Har1)-ethyl, in which

Har1 is pyridin-3-yl, pyridin-4-yl, indol-3-yl, or indol-5-yl, and

R612 is hydrogen,

or

T2 is methylene,

R611 is methyl, or 2-(Har1)-ethyl, in which

Har1 is indol-2-yl, and

R612 is methyl,

or

T2 is methylene,

R611 is 2-(Har1)-ethyl, in which

Har1 is indol-2-yl, and

R612 is 2-hydroxy-ethyl,

or

T2 is methylene, and

R611 and R612 together and with inclusion of the nitrogen atom, to which they are bonded, form a heterocyclic ring Het1, in which

Het1 is morpholino,

Aa1 is 1,1'-biphen-4-yl or 1,1'-biphen-3-yl,  
Hh1 is 5-(pyridin-2-yl)-thiophen-2-yl,  
Ah1 is 3-(pyridin-3-yl)-phenyl, 3-(pyridin-4-yl)-phenyl, 3-(pyrazol-1-yl)-phenyl, 3-(1H-pyrazol-4-yl)-phenyl, 4-(pyridin-3-yl)-phenyl, 4-(pyridin-4-yl)-phenyl, 4-(pyrazol-1-yl)-phenyl or 4-(1H-pyrazol-4-yl)-phenyl,  
R7 is 2-aminophenyl,  
and the salts of these compounds.

A special interest in the compounds according to the present invention refers to those compounds of this invention which are included -within the scope of this invention- by one or, when possible, a combination of more of the following embodiments:

An embodiment of the compounds according to the present invention relates to those compounds of formula I, in which R1, R2, R3, R4 and R5 are all hydrogen.

A further embodiment of the compounds according to the present invention relates to those compounds of formula I, in which R7 is hydroxyl.

A further embodiment of the compounds according to the present invention relates to those compounds of formula I, in which R7 is Cyc1, whereby in a subembodiment thereof Cyc1 is 2-phenyl.

A further embodiment of the compounds according to the present invention relates to those compounds of formula I, in which R7 is 2-aminophenyl.

A further embodiment of the compounds according to the present invention relates to those compounds of formula I, in which R6 is Aa1.

A further embodiment of the compounds according to the present invention relates to those compounds of formula I, in which R6 is Ar1 or -CH<sub>2</sub>-Ar1.

A further embodiment of the compounds according to the present invention relates to those compounds of formula I, in which Ar1 is R61-substituted phenyl.

A further embodiment of the compounds according to the present invention relates to those compounds of formula I, in which Ar1 is phenyl monosubstituted by R61 in the meta position with respect to the binding position in which the phenyl ring is bonded to T1.

A further embodiment of the compounds according to the present invention relates to those compounds of formula I, in which Ar1 is phenyl monosubstituted by R61 in the para position with respect to the binding position in which the phenyl ring is bonded to T1.

A further embodiment of the compounds according to the present invention relates to those compounds of formula I, in which R6 is Hh1.

A further embodiment of the compounds according to the present invention relates to those compounds of formula I, in which R6 is Ah1.

A further embodiment of the compounds according to the present invention relates to those compounds of formula I, in which T2 is a bond.

A further embodiment of the compounds according to the present invention relates to those compounds of formula I, in which T2 is 1-4C-alkylene, such as e.g. methylene.

A further embodiment of the compounds according to the present invention relates to those compounds of formula I, in which

R6 is Ar1, in which  
Ar1 is R61-substituted phenyl, in which  
R61 is -T2-N(R611)R612, in which  
T2 is a bond.

A further embodiment of the compounds according to the present invention relates to those compounds of formula I, in which

R6 is Ar1, in which  
Ar1 is R61-substituted phenyl, in which  
R61 is -T2-N(R611)R612, in which  
T2 is 1-4C-alkylene, such as e.g. methylene.

A further embodiment of the compounds according to the present invention relates to those compounds of formula I, in which

R1, R2, R3, R4 and R5 are all hydrogen, and  
R6 is Ar1, in which  
Ar1 is any one selected from the group consisting of  
3-methyl-phenyl, 4-methyl-phenyl,  
3-dimethylamino-phenyl, 4-dimethylamino-phenyl,  
3-aminomethyl-phenyl, 4-aminomethyl-phenyl,  
3-(morpholin-4-yl-methyl)-phenyl, 4-(morpholin-4-yl-methyl)-phenyl,  
3-(N-benzylamino-methyl)-phenyl, 3-(N-isobutylamino-methyl)-phenyl,

4-(N-benzylamino-methyl)-phenyl, 4-(N-isobutylamino-methyl)-phenyl,  
3-[N-(pyridinylmethyl)amino-methyl]-phenyl, 3-[N-(indolylmethyl)amino-methyl]-phenyl,  
4-[N-(pyridinylmethyl)amino-methyl]-phenyl, 4-[N-(indolylmethyl)amino-methyl]-phenyl,  
3-(N,N-dimethylamino-methyl)-phenyl, 4-(N,N-dimethylamino-methyl)-phenyl,  
3-[N,N-(2-indolyethyl)-methyl-amino-methyl]-phenyl, 4-[N,N-(2-indolyethyl)-methyl-amino-methyl]-  
phenyl,  
3-[N,N-(2-indolyethyl)-(2-hydroxyethyl)-amino-methyl]-phenyl, and 4-[N,N-(2-indolyethyl)-(2-  
hydroxyethyl)-amino-methyl]-phenyl.

A further embodiment of the compounds according to the present invention relates to those compounds of formula I, in which

R1, R2, R3, R4 and R5 are all hydrogen, and

R6 is Aa1, in which

Aa1 is a biphenyl radical.

A further embodiment of the compounds according to the present invention relates to those compounds of formula I, in which

R1, R2, R3, R4 and R5 are all hydrogen, and

R6 is Ha1, in which

Ha1 is a pyridinyl-thiophenyl radical.

A further embodiment of the compounds according to the present invention relates to those compounds of formula I, in which

R1, R2, R3, R4 and R5 are all hydrogen, and

R6 is Ah1, in which

Ah1 is a 3-(pyrazolyl)-phenyl, 4-(pyrazolyl)-phenyl, 4-(pyridinyl)-phenyl, or 3-(pyridinyl)-phenyl radical.

A further embodiment of the compounds according to the present invention relates to those compounds of formula I, in which R1, R2, R3, R4 and R5 are all hydrogen, and R7 is hydroxyl.

A further embodiment of the compounds according to the present invention relates to those compounds of formula I, in which R1, R2, R3, R4 and R5 are all hydrogen, and R7 is Cyc1.

A further embodiment of the compounds according to the present invention relates to those compounds of formula I, in which R1, R2, R3, R4 and R5 are all hydrogen, and R7 is 2-aminophenyl.

A further embodiment of the compounds according to the present invention relates to those compounds of formula I, in which R1, R2, R3, R4 and R5 are all hydrogen, and R7 is aminopyridyl.

- 27 -

A special embodiment of the compounds according to the present invention relates to those compounds of formula I, in which

R1, R2, R3, R4 and R5 are all hydrogen, and

R6 is Ar1, in which

Ar1 is any one selected from the group consisting of

3-methyl-phenyl, 4-methyl-phenyl,

3-dimethylamino-phenyl, 4-dimethylamino-phenyl,

3-aminomethyl-phenyl, 4-aminomethyl-phenyl,

3-(morpholin-4-yl-methyl)-phenyl, 4-(morpholin-4-yl-methyl)-phenyl,

3-(N-benzylamino-methyl)-phenyl, 3-(N-isobutylamino-methyl)-phenyl,

4-(N-benzylamino-methyl)-phenyl, 4-(N-isobutylamino-methyl)-phenyl,

3-[N-(pyridin-3-yl-methyl)amino-methyl]-phenyl, 3-[N-(pyridin-4-yl-methyl)amino-methyl]-phenyl,

3-[N-(indol-5-yl-methyl)amino-methyl]-phenyl, 3-[N-(indol-3-yl-methyl)amino-methyl]-phenyl,

4-[N-(pyridin-3-yl-methyl)amino-methyl]-phenyl, 4-[N-(pyridin-4-yl-methyl)amino-methyl]-phenyl,

4-[N-(indol-5-yl-methyl)amino-methyl]-phenyl, 4-[N-(indol-3-yl-methyl)amino-methyl]-phenyl,

3-(N,N-dimethylamino-methyl)-phenyl, 4-(N,N-dimethylamino-methyl)-phenyl,

3-{N,N-[2-(indol-2-yl)-ethyl]-methyl-amino-methyl}-phenyl, 4-{N,N-[2-(indol-2-yl)-ethyl]-methyl-amino-methyl}-phenyl,

3-{N,N-[2-(indol-2-yl)-ethyl]-(2-hydroxyethyl)-amino-methyl}-phenyl, and 4-{N,N-[2-(indol-2-yl)-ethyl]-(2-hydroxyethyl)-amino-methyl}-phenyl, and

R7 is hydroxyl,

and the salts thereof.

Another special embodiment of the compounds according to the present invention relates to those compounds of formula I, in which

R1, R2, R3, R4 and R5 are all hydrogen, and

R6 is Aa1, in which

Aa1 is 1,1'-biphen-4-yl or 1,1'-biphen-3-yl, and

R7 is hydroxyl,

and the salts thereof.

Another special embodiment of the compounds according to the present invention relates to those compounds of formula I, in which

R1, R2, R3, R4 and R5 are all hydrogen, and

R6 is Ha1, in which

Ha1 is 5-(pyridin-2-yl)-thiophen-2-yl, and

R7 is hydroxyl,

and the salts thereof.

Another special embodiment of the compounds according to the present invention relates to those compounds of formula I, in which

R1, R2, R3, R4 and R5 are all hydrogen, and

R6 is Ah1, in which

Ah1 is 3-(pyrazol-1-yl)-phenyl, 4-(pyrazol-1-yl)-phenyl, 4-(pyridin-4-yl)-phenyl, 3-(pyridin-4-yl)-phenyl, 4-(pyridin-3-yl)-phenyl, 3-(pyridin-3-yl)-phenyl, 3-(1H-pyrazol-4-yl)-phenyl or 4-(1H-pyrazol-4-yl)-phenyl,

R7 is hydroxyl,

and the salts thereof.

Another special embodiment of the compounds according to the present invention relates to those compounds of formula I, in which

R1, R2, R3, R4 and R5 are all hydrogen, and

R6 is Ar1, in which

Ar1 is any one selected from the group consisting of

3-methyl-phenyl, 4-methyl-phenyl,

3-dimethylamino-phenyl, 4-dimethylamino-phenyl,

3-aminomethyl-phenyl, 4-aminomethyl-phenyl,

3-(morpholin-4-yl-methyl)-phenyl, 4-(morpholin-4-yl-methyl)-phenyl,

3-(N-benzylamino-methyl)-phenyl, 3-(N-isobutylamino-methyl)-phenyl,

4-(N-benzylamino-methyl)-phenyl, 4-(N-isobutylamino-methyl)-phenyl,

3-[N-(pyridin-3-yl-methyl)amino-methyl]-phenyl, 3-[N-(pyridin-4-yl-methyl)amino-methyl]-phenyl,

3-[N-(indol-5-yl-methyl)amino-methyl]-phenyl, 3-[N-(indol-3-yl-methyl)amino-methyl]-phenyl,

4-[N-(pyridin-3-yl-methyl)amino-methyl]-phenyl, 4-[N-(pyridin-4-yl-methyl)amino-methyl]-phenyl,

4-[N-(indol-5-yl-methyl)amino-methyl]-phenyl, 4-[N-(indol-3-yl-methyl)amino-methyl]-phenyl,

3-(N,N-dimethylamino-methyl)-phenyl, 4-(N,N-dimethylamino-methyl)-phenyl,

3-{N,N-[2-(indol-2-yl)-ethyl]-methyl-amino-methyl}-phenyl, 4-{N,N-[2-(indol-2-yl)-ethyl]-methyl-amino-methyl}-phenyl,

3-{N,N-[2-(indol-2-yl)-ethyl]-(2-hydroxyethyl)-amino-methyl}-phenyl, and 4-{N,N-[2-(indol-2-yl)-ethyl]-(2-hydroxyethyl)-amino-methyl}-phenyl, and

R7 is 2-aminophenyl,

and the salts thereof.

Another special embodiment of the compounds according to the present invention relates to those compounds of formula I, in which

R1, R2, R3, R4 and R5 are all hydrogen, and

R6 is Aa1, in which

Aa1 is 1,1'-biphen-4-yl or 1,1'-biphen-3-yl, and

R7 is 2-aminophenyl,

and the salts thereof.



Another special embodiment of the compounds according to the present invention relates to those compounds of formula I, in which

R1, R2, R3, R4 and R5 are all hydrogen, and

R6 is Ha1, in which

Ha1 is 5-(pyridin-2-yl)-thiophen-2-yl, and

R7 is 2-aminophenyl,

and the salts thereof.

Another special embodiment of the compounds according to the present invention relates to those compounds of formula I, in which

R1, R2, R3, R4 and R5 are all hydrogen, and

R6 is Ah1, in which

Ah1 is 3-(pyrazol-1-yl)-phenyl, 4-(pyrazol-1-yl)-phenyl, 4-(pyridin-4-yl)-phenyl, 3-(pyridin-4-yl)-phenyl, 4-(pyridin-3-yl)-phenyl, 3-(pyridin-3-yl)-phenyl, 3-(1H-pyrazol-4-yl)-phenyl or 4-(1H-pyrazol-4-yl)-phenyl,

R7 is 2-aminophenyl,

and the salts thereof.

Exemplary compounds according to this invention may include any one selected from

1. (E)-N-Hydroxy-3-[1-(toluene-4-sulfonyl)-1H-pyrrol-3-yl]-acrylamide
2. N-Hydroxy-3-(1-phenylmethanesulfonyl-1H-pyrrol-3-yl)-acrylamide
3. (E)-3-[1-(Biphenyl-4-sulfonyl)-1H-pyrrol-3-yl]-N-hydroxy-acrylamide
4. (E)-3-[1-(4-Dimethylamino-benzenesulfonyl)-1H-pyrrol-3-yl]-N-hydroxy-acrylamide
5. (E)-N-(2-Amino-phenyl)-3-[1-(toluene-4-sulfonyl)-1H-pyrrol-3-yl]-acrylamide
6. (E)-N-(2-Amino-phenyl)-3-(1-phenylmethanesulfonyl-1H-pyrrol-3-yl)-acrylamide
7. (E)-N-(2-Amino-phenyl)-3-[1-(biphenyl-4-sulfonyl)-1H-pyrrol-3-yl]-acrylamide
8. (E)-N-(2-Amino-phenyl)-3-[1-(4-dimethylamino-benzenesulfonyl)-1H-pyrrol-3-yl]-acrylamide
9. (E)-N-Hydroxy-3-(1-[4-((2-(1H-indol-2-yl)-ethyl)-methyl-amino)-methyl]-benzene sulfonyl]-1H-pyrrol-3-yl)-acrylamide
10. (E)-3-[1-(4-Dimethylaminomethyl-benzenesulfonyl)-1H-pyrrol-3-yl]-N-hydroxy-acrylamide
11. (E)-N-Hydroxy-3-[1-(4-[(pyridin-3-ylmethyl)-amino]-methyl)-benzenesulfonyl]-1H-pyrrol-3-yl]-acrylamide
12. (E)-N-Hydroxy-3-[1-(4-[(1H-indol-3-ylmethyl)-amino]-methyl)-benzenesulfonyl]-1H-pyrrol-3-yl]-acrylamide
13. (E)-3-[1-(4-(Benzylamino-methyl)-benzenesulfonyl)-1H-pyrrol-3-yl]-N-hydroxy-acrylamide
14. (E)-N-Hydroxy-3-[1-(4-(isobutylamino-methyl)-benzenesulfonyl)-1H-pyrrol-3-yl]-acrylamide
15. (E)-N-Hydroxy-3-[1-(4-[(1H-indol-5-ylmethyl)-amino]-methyl)-benzenesulfonyl]-1H-pyrrol-3-yl]-acrylamide

16. (E)-N-Hydroxy-3-[1-(4-[(pyridin-4-ylmethyl)-amino]-methyl)-benzenesulfonyl]-1H-pyrrol-3-yl]-acrylamide
17. (E)-3-[1-(4-Aminomethyl-benzenesulfonyl)-1H-pyrrol-3-yl]-N-hydroxy-acrylamide
18. (E)-N-Hydroxy-3-[1-(4-pyridin-4-yl-benzenesulfonyl)-1H-pyrrol-3-yl]-acrylamide
19. (E)-N-Hydroxy-3-{1-[4-(1H-pyrazol-4-yl)-benzenesulfonyl]-1H-pyrrol-3-yl}-acrylamide
20. (E)-N-(2-Amino-phenyl)-3-[1-(4-pyridin-4-yl-benzenesulfonyl)-1H-pyrrol-3-yl]-acrylamide
21. (E)-N-(2-Amino-phenyl)-3-[1-(4-pyridin-3-yl-benzenesulfonyl)-1H-pyrrol-3-yl]-acrylamide
22. (E)-N-(2-Amino-phenyl)-3-{1-[4-(1H-pyrazol-4-yl)-benzenesulfonyl]-1H-pyrrol-3-yl}-acrylamide
23. (E)-3-[1-(Biphenyl-3-sulfonyl)-1H-pyrrol-3-yl]-N-hydroxy-acrylamide
24. (E)-N-Hydroxy-3-[1-(5-pyridin-2-yl-thiophene-2-sulfonyl)-1H-pyrrol-3-yl]-acrylamide
25. (E)-N-Hydroxy-3-[1-(4-pyrazol-1-yl-benzenesulfonyl)-1H-pyrrol-3-yl]-acrylamide
26. (E)-N-(2-Amino-phenyl)-3-[1-(5-pyridin-2-yl-thiophene-2-sulfonyl)-1H-pyrrol-3-yl]-acrylamide
27. (E)-N-Hydroxy-3-[1-(4-morpholin-4-ylmethyl-benzenesulfonyl)-1H-pyrrol-3-yl]-acrylamide
28. (E)-N-Hydroxy-3-{1-[4-[(2-hydroxy-ethyl)-[2-(1H-indol-2-yl)-ethyl]-amino]-methyl]-benzenesulfonyl]-1H-pyrrol-3-yl}-acrylamide
29. (E)-N-Hydroxy-3-[1-(3-pyridin-4-yl-benzenesulfonyl)-1H-pyrrol-3-yl]-acrylamide
30. (E)-N-(2-Amino-phenyl)-3-[1-(3-pyridin-4-yl-benzenesulfonyl)-1H-pyrrol-3-yl]-acrylamide
31. (E)-N-(2-Amino-phenyl)-3-[1-(3-pyridin-3-yl-benzenesulfonyl)-1H-pyrrol-3-yl]-acrylamide
32. (E)-N-Hydroxy-3-{1-[3-(1H-pyrazol-4-yl)-benzenesulfonyl]-1H-pyrrol-3-yl}-acrylamide and
33. (E)-N-(2-Amino-phenyl)-3-{1-[3-(1H-pyrazol-4-yl)-benzenesulfonyl]-1H-pyrrol-3-yl}-acrylamide, and the salts thereof.

In a particular embodiment of aspect 3, the present invention provides salts of (E)-3-[1-(4-dimethylaminomethyl-benzenesulfonyl)-1H-pyrrol-3-yl]-N-hydroxy-acrylamide with hydrochloric acid, particularly being in crystalline form, their hydrates, as well as specific polymorphs and mixtures thereof.

In another particular embodiment of aspect 3, the present invention relates to (E)-3-[1-(4-dimethylaminomethyl-benzenesulfonyl)-1H-pyrrol-3-yl]-N-hydroxy-acrylamide hydrochloride, particularly being in crystalline form, as well as to specific polymorphs and mixtures thereof.

In another particular embodiment of aspect 3, the present invention relates to hydrochloride salts of (E)-3-[1-(4-dimethylaminomethyl-benzenesulfonyl)-1H-pyrrol-3-yl]-N-hydroxy-acrylamide, particularly being in crystalline form, hydrates and specific polymorphs thereof.

In another particular embodiment of aspect 3, the present invention relates to specific polymorphs of hydrochloride salts of (E)-3-[1-(4-dimethylaminomethyl-benzenesulfonyl)-1H-pyrrol-3-yl]-N-hydroxy-acrylamide, and hydrates thereof.

In another particular embodiment of aspect 3, the present invention relates to (E)-3-[1-(4-dimethylaminomethyl-benzenesulfonyl)-1H-pyrrol-3-yl]-N-hydroxy-acrylamide mono-hydrochloride, particularly being in crystalline form, as well as to specific polymorphs and mixtures thereof.

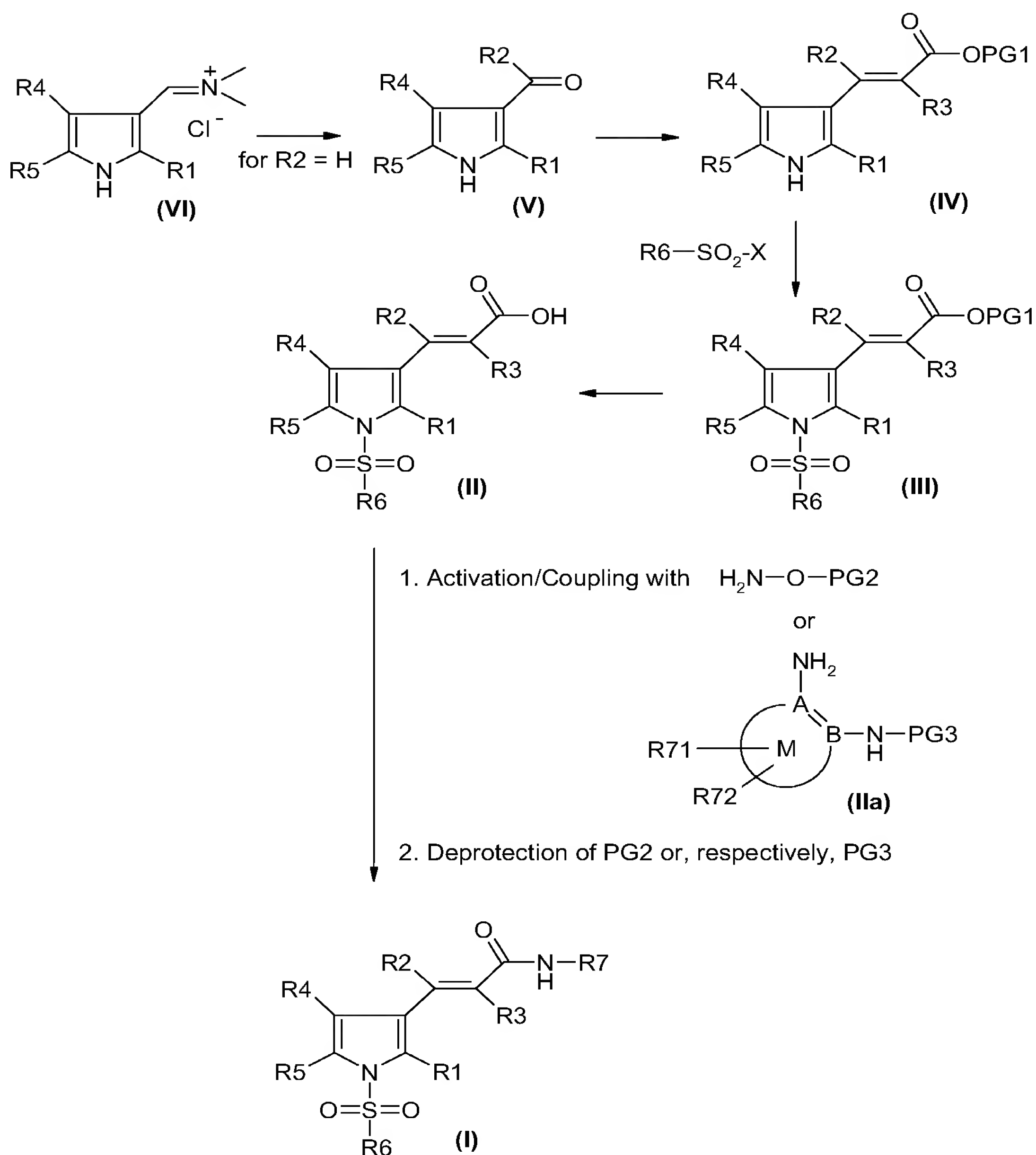
In yet another particular embodiment of aspect 3, the present invention relates to (E)-N-hydroxy-3-[1-(5-pyridin-2-yl-thiophene-2-sulfonyl)-1H-pyrrol-3-yl]-acrylamide hydrochloride.

The compounds according to the present invention can be prepared, for example, as shown in the reaction schemes below and according to the reaction steps specified as follows, or, particularly, in a manner as described by way of example in the following examples, or analogously or similarly thereto using preparation procedures and synthesis strategies known to the person skilled in the art.

In reaction scheme 1 the carbon chain of compounds of formula V, in which R1, R2, R4 and R5 have the meanings mentioned above, is lengthened, for example, by a condensation reaction (with a malonic acid derivative) or by a Wittig or Julia reaction or, particularly in the case when R2 is hydrogen, by a Horner-Wadsworth-Emmons reaction (with a  $\beta$ -(alkoxycarbonyl)-phosphonic acid dialkyl ester) to obtain compounds of formula IV, in which R1, R2, R3, R4 and R5 have the meanings mentioned above and PG1 stands for a suitable temporary protective group for the carboxyl group, for example tert-butyl or one of those art-known protective groups mentioned in "Protective Groups in Organic Synthesis" by T. Greene and P. Wuts (John Wiley & Sons, Inc. 1999, 3<sup>rd</sup> Ed.) or in "Protecting Groups (Thieme Foundations Organic Chemistry Series N Group" by P. Kocienski (Thieme Medical Publishers, 2000).

Reaction scheme 1

- 32 -



Compounds of formula V, in which R1, R2, R4 and R5 have the meanings mentioned above, are known, or can be prepared according to art-known procedures, or can be obtained as described in the following examples for the case that R2 is hydrogen from compounds of formula VI.

Compounds of formula VI are known or are accessible in a known manner or as described in the following examples.

Compounds of formula IV, in which R1, R2, R3, R4 and R5 have the meanings mentioned above and PG1 stands for a said suitable protective group, can be reacted with compounds of formula  $\text{R6-SO}_2\text{-}$

X, in which R6 has the meanings mentioned above and X is a suitable leaving group, such as e.g. chlorine, to give the corresponding compounds of formula III.

In the next reaction step, the protective group PG1 of compounds of formula III can be removed in a manner as described in the following examples or according to an art-known manner to afford compounds of formula II.

Compounds of formula R6-SO<sub>2</sub>-X are known or can be prepared in a known manner.

Compounds of formula II, in which R1, R2, R3, R4, R5 and R6 have the meanings given above, can be coupled with compounds of formulae H<sub>2</sub>N-O-PG2, in which PG2 is a suitable oxygen protective group such as e.g. a suitable silyl or tetrahydropyran-2-yl protective group, or IIa, in which PG3 stands for a suitable nitrogen protective group such as e.g. the tert-butyloxycarbonyl protective group, by reaction with amide bond linking reagents optionally in the presence of coupling additives known to the person skilled in the art. Exemplary amide bond linking reagents known to the person skilled in the art which may be mentioned are, for example, carbodiimides (e.g. dicyclohexylcarbodiimide or, preferably, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride), azodicarboxylic acid derivatives (e.g. diethyl azodicarboxylate), uronium salts [e.g. O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate or O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium-hexafluorophosphate] and N,N'-carbonyldiimidazole.

Alternatively, compounds of formula II can be activated prior to the coupling reaction by forming an acid halide or acid anhydride optionally in an in-situ procedure without isolating the acid halide or acid anhydride.

Compounds of formulae H<sub>2</sub>N-O-PG2 or IIa are known or can be prepared according to art-known processes.

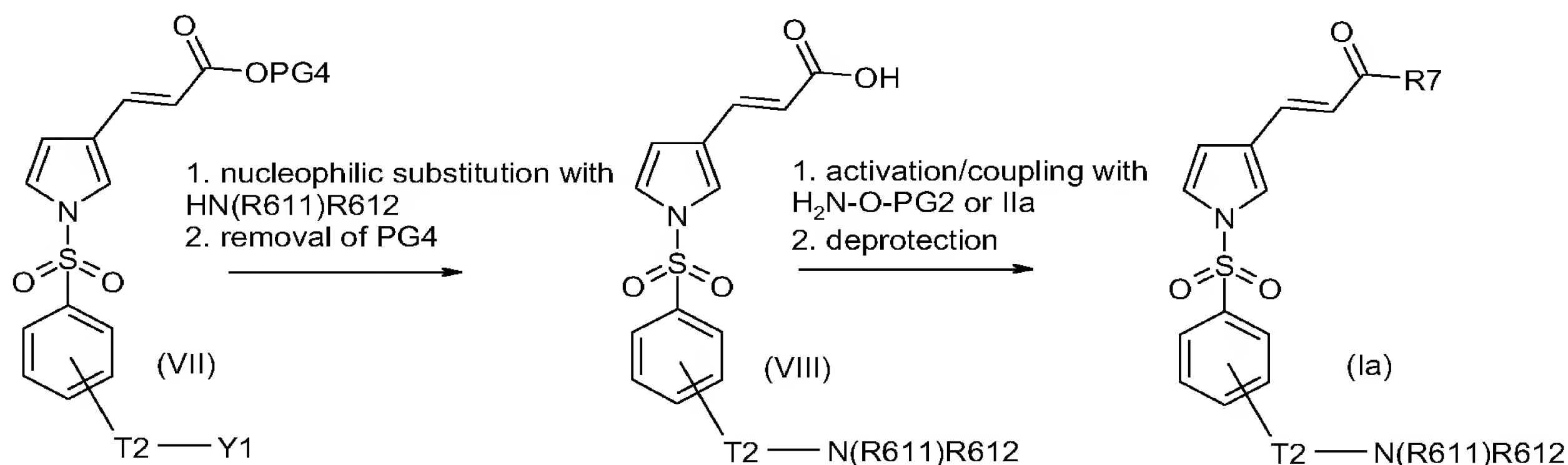
Removal of the protective groups PG2 or PG3 can be obtained in a manner known for the person skilled in the art or as described in the following examples to give compounds of formula I, in which R1, R2, R3, R4, R5, R6 and R7 have the meanings mentioned above.

Compounds of formula I, in which T2 is 1-4C-alkylene, particularly methylene, can be prepared as outlined in the following reaction schemes 2 to 5, and specified below, or as described by way of example in the following examples, or analogously or similarly thereto.

As shown in reaction scheme 2 compounds of formula VII, in which T2 is 1-4C-alkylene, particularly methylene, and Y1 is a suitable leaving group, such as e.g. iodine, chlorine or, particularly, bromine, and PG4 stands for a suitable temporary protective group for the carboxyl group, for example tert-butyl, can be reacted with compounds of formula HN(R611)R612 to give in an art-known nucleophilic

substitution reaction corresponding amino compounds, which are deprotected by removal of PG4 to give corresponding free acids of formula VIII, which can be coupled with compounds of formulae  $\text{H}_2\text{N-O-PG2}$  or IIa as described above to give, after removal of PG2 and PG3, corresponding compounds of formula Ia.

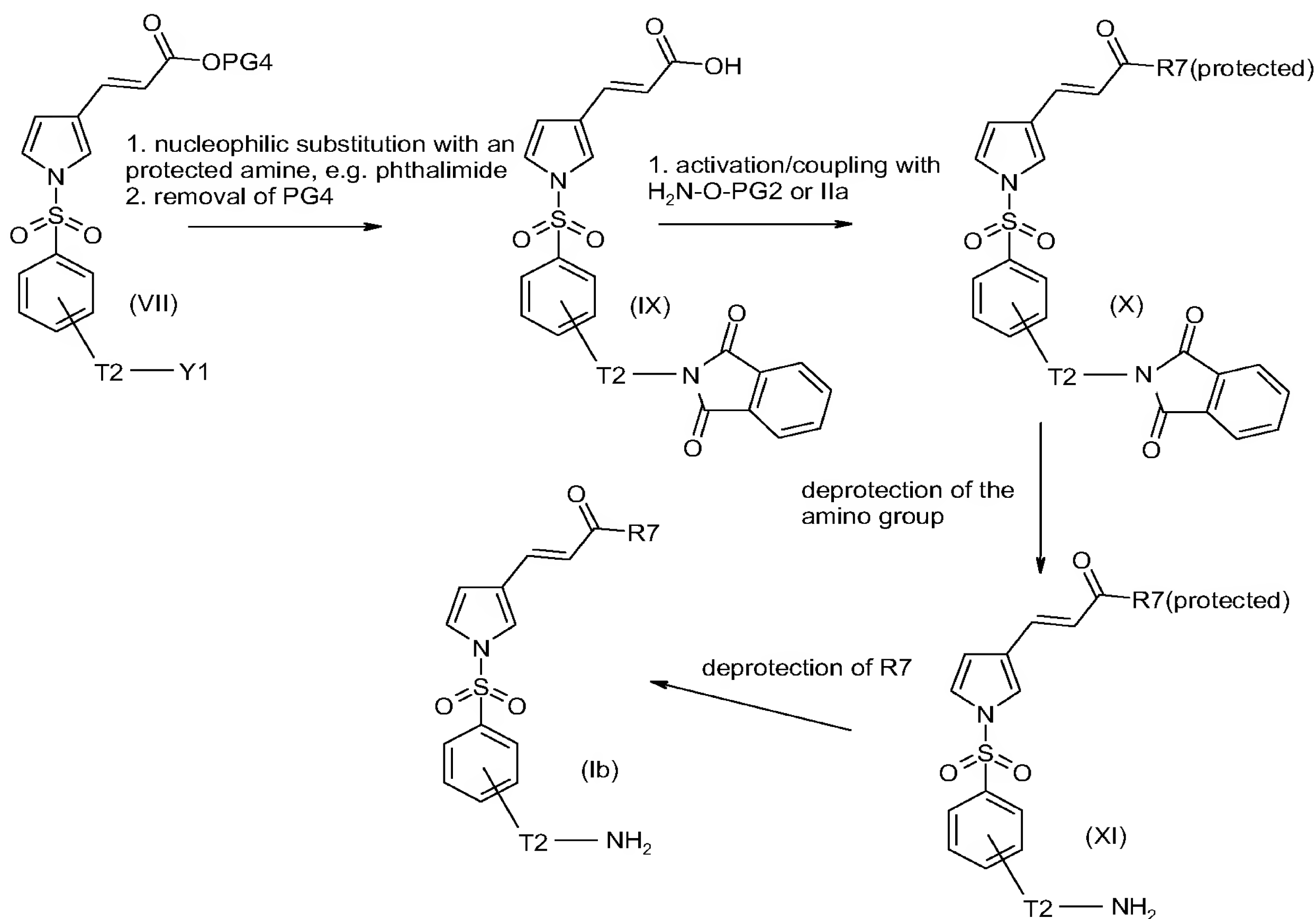
Reaction scheme 2:



Alternatively, as shown in reaction scheme 3, compounds of formula VII, in which T2 is 1-4C-alkylene, particularly methylene, and Y1 is a suitable leaving group, such as e.g. iodine, chlorine or, particularly, bromine, and PG4 stands for a suitable temporary protective group for the carboxyl group, for example tert-butyl, can be reacted with a temporarily protected amine (a primary or, particularly, a secondary one), such as e.g. phthalimide, to give in an art-known nucleophilic substitution reaction corresponding amino compounds, which are deprotected by removal of PG4 to give corresponding free acids of formula IX, which can be coupled with compounds of formulae  $\text{H}_2\text{N-O-PG2}$  or IIa as described above to give corresponding compounds of formula X.

Reaction scheme 3:

- 35 -



The amino moiety of compounds of formula X can be deprotected in an art-known manner to give corresponding compounds of formula XI, such as e.g. when the phthalimido protective group is used, this can be removed in a manner customary per se to the skilled person, e.g. with the aid of hydrazine.

Compounds of formula XI can be deprotected to give corresponding compounds of formula Ib.

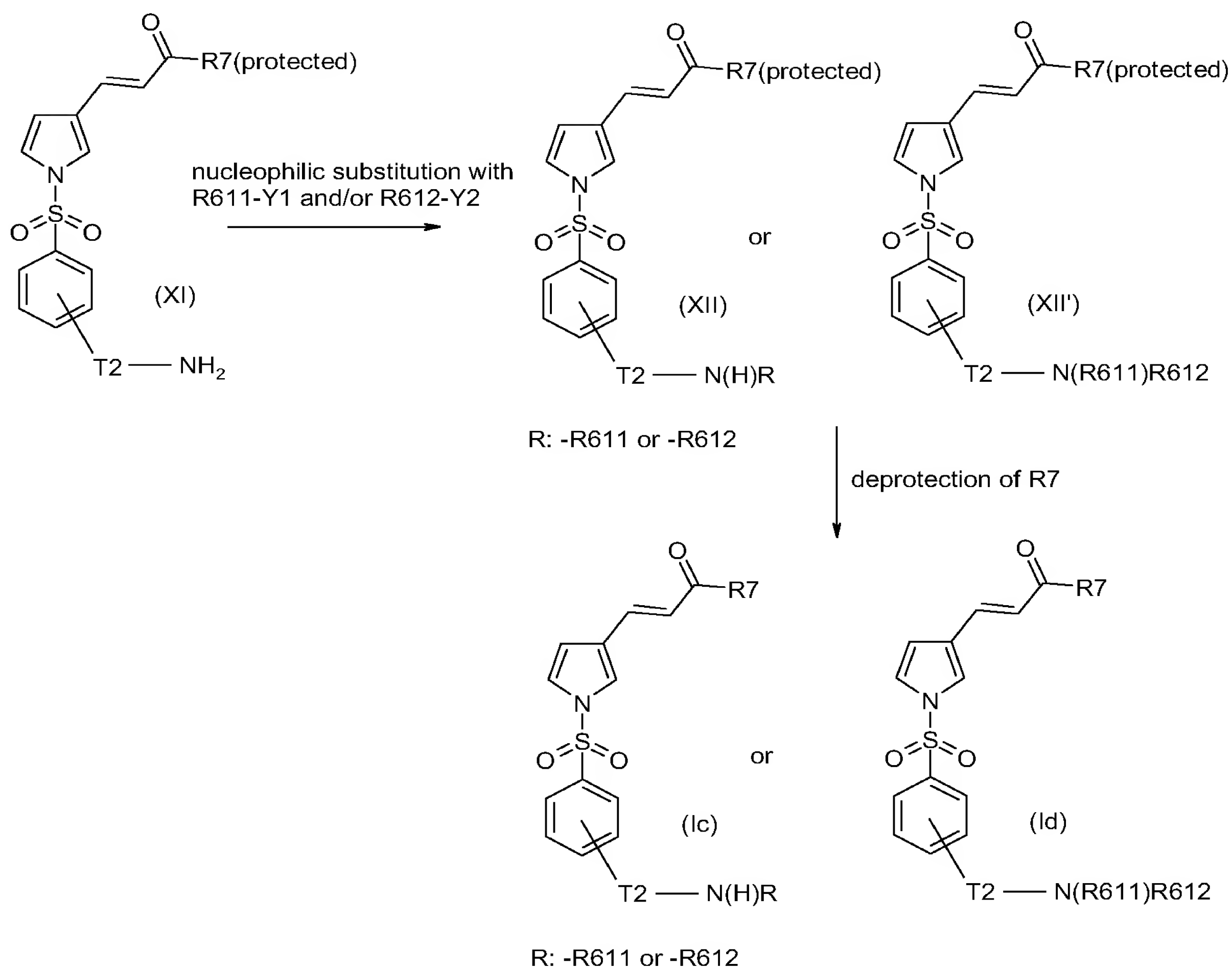
Alternatively, as shown in reaction scheme 4, compounds of formula XI can be reacted with compounds of formula  $\text{R611}-\text{Y1}$  and/or  $\text{R612}-\text{Y2}$ , in which  $\text{R611}$  and  $\text{R612}$  have the meanings given above and are different from hydrogen and  $\text{Y1}$  and  $\text{Y2}$  are suitable leaving groups such as e.g. chlorine, bromine, iodine or a sulfonate (e.g. triflate) leaving group, to give in an art-known nucleophilic substitution reaction corresponding compounds of formula XII or XII'.

Compounds of formula XII or XII' can be deprotected to give corresponding compounds of formula Ic or Id, respectively.

Reaction scheme 4:



- 36 -

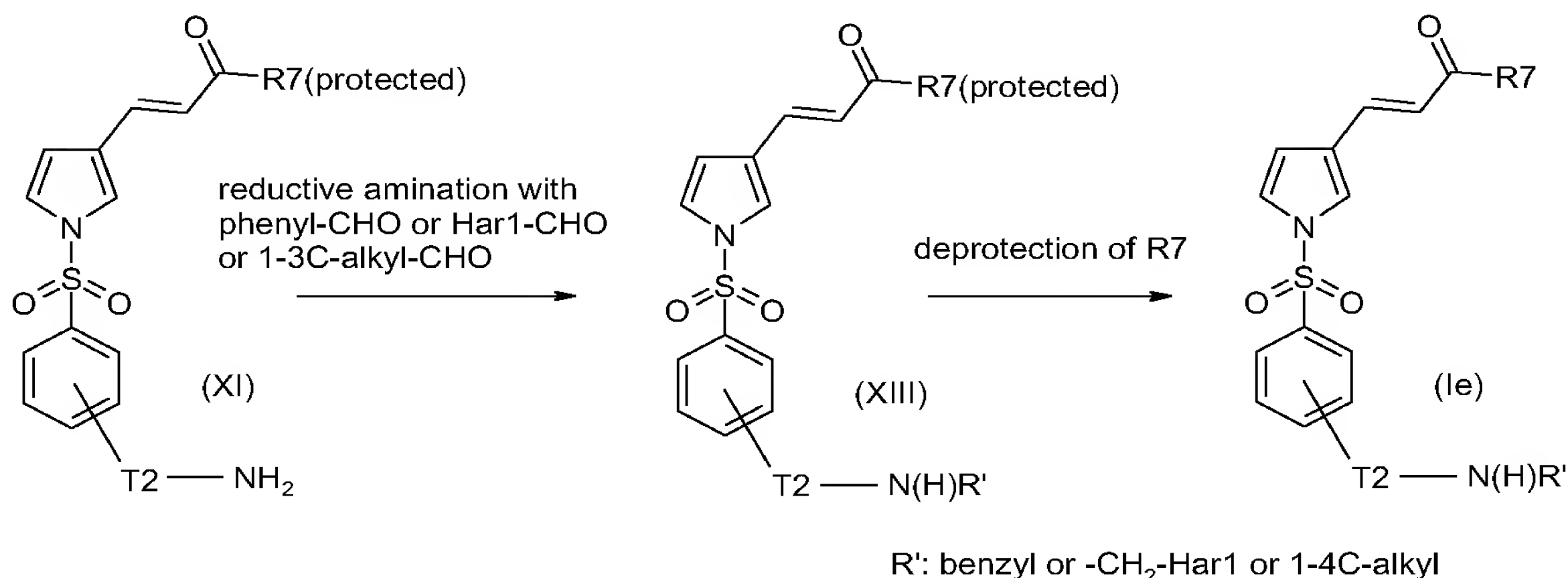


Yet alternatively, as shown in reaction scheme 5, compounds of formula XI can be reacted with aldehydes or ketones in an reductive amination reaction, such as e.g. compounds of formula XI can be reacted with benzaldehyde, or compounds of formulae  $1\text{-}3\text{C-alkyl-CHO}$  or  $\text{Har1-CHO}$ , in which Har1 has the meanings given above, to give in an art-known reductive amination reaction corresponding compounds of formula XIII.

Compounds of formula XIII can be deprotected to give corresponding compounds of formula Ie.

Reaction scheme 5:

- 37 -

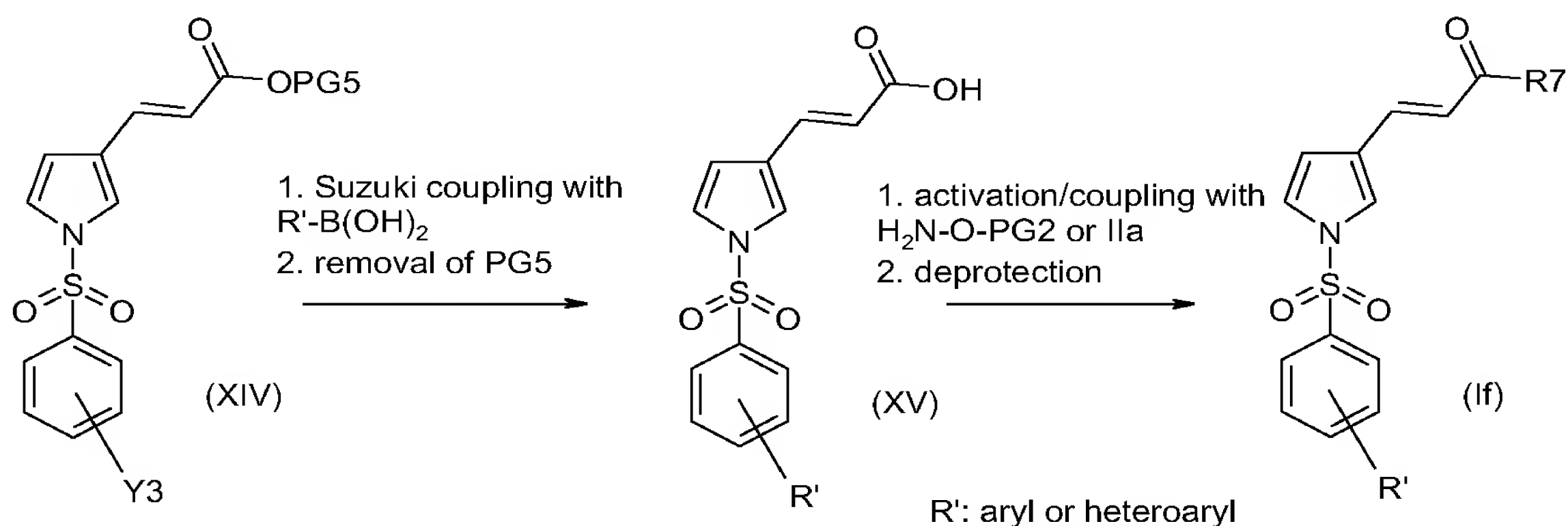


Compounds of formula VII can be obtained according to the synthesis route shown in reaction scheme 1 and described above.

The abovementioned compounds of formulae HN(R611)R612, R611-Y1, R612-Y2, 1-3C-alkyl-CHO or Har1-CHO are known or can be obtained according to art-known procedures.

Compounds of formula I, in which R6 is Aa1 or Ah1, can be prepared as outlined in the following reaction scheme 6, and specified below, or as described by way of example in the following examples, or analogously or similarly thereto.

Reaction scheme 6:

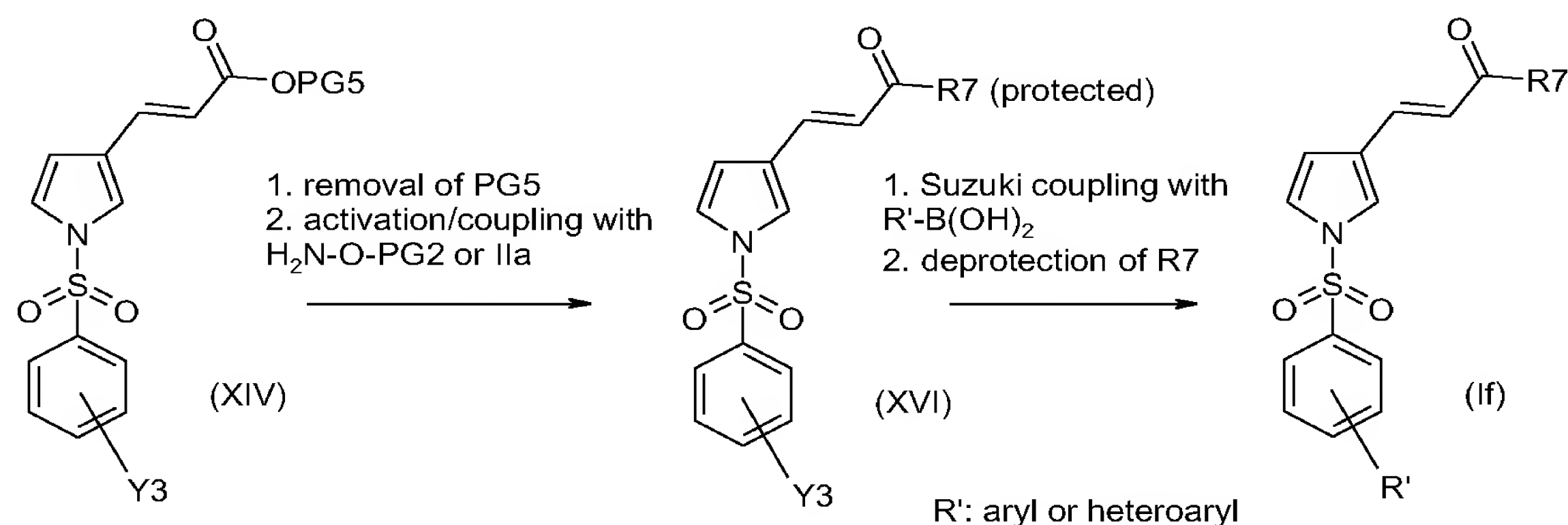


As shown in reaction scheme 6 compounds of formula XIV, in which Y3 is a suitable leaving group, such as e.g. iodine or bromine, and PG5 stands for a suitable temporary protective group for the carboxyl group, for example tert-butyl, can be reacted with boronic acids of formula R'-B(OH)<sub>2</sub>, in which R' is the terminal aryl or heteroaryl moiety of the abovementioned Aa1 or Ha1 radicals, or the boronic acid esters (e.g. the pinacol esters) thereof, to give in an art-known Suzuki reaction the corresponding CC-coupled compounds, which are deprotected by removal of PG5 to give corresponding free acids of formula XV, which can be coupled with compounds of formulae H<sub>2</sub>N-O-

PG2 or IIa as described above to give, after removal of PG2 and PG3, corresponding compounds of formula If.

Alternatively, as shown in reaction scheme 7 compounds of formula XIV, in which Y3 is a suitable leaving group, such as e.g. iodine or bromine, and PG5 stands for a suitable temporary protective group for the carboxyl group, for example tert-butyl, can be deprotected by removal of PG5, and the free carboxylic acid can be then coupled with compounds of formulae  $\text{H}_2\text{N-O-PG2}$  or IIa as described above to give corresponding compounds of formula XVI. Compounds of formula XVI are reacted with boronic acids of formula  $\text{R}'\text{-B(OH)}_2$ , in which  $\text{R}'$  is the terminal aryl or heteroaryl moiety of the abovementioned Aa1 or Ha1 radicals, or the boronic acid esters (e.g. the pinacol esters) thereof, to give in an art-known Suzuki reaction the corresponding CC-coupled compounds, which are deprotected by removal of PG2 or PG3 to give corresponding compounds of formula If.

Reaction scheme 7:



The Suzuki reaction can be carried out in a manner habitual per se to the skilled person or as described in the following examples, or analogously or similarly thereto.

Compounds of formula XIV can be obtained according to the synthesis route shown in reaction scheme 1 and described above.

The abovementioned compounds of formula  $\text{R}'\text{-B(OH)}_2$  are known or can be obtained according to art-known procedures.

The reactions mentioned above can be expediently carried out analogously to the methods known to the person skilled in the art or as described by way of example in the following examples.

It is moreover known to the person skilled in the art that if there are a number of reactive centers on a starting or intermediate compound it may be necessary to block one or more reactive centers temporarily by protective groups in order to allow a reaction to proceed specifically at the desired

reaction center. A detailed description for the use of a large number of proven protective groups is found, for example, in "Protective Groups in Organic Synthesis" by T. Greene and P. Wuts (John Wiley & Sons, Inc. 1999, 3<sup>rd</sup> Ed.) or in "Protecting Groups (Thieme Foundations Organic Chemistry Series N Group" by P. Kocienski (Thieme Medical Publishers, 2000).

The isolation and purification of the substances according to the invention is carried out in a manner known per se, e.g. by distilling off the solvent in vacuo and recrystallizing the resulting residue from a suitable solvent or subjecting it to one of the customary purification methods, such as, for example, column chromatography on suitable support material.

Optionally, compounds of formula I can be converted into their salts, or, optionally, salts of the compounds of formula I can be converted into the free compounds.

Salts are obtained by dissolving the free compound in a suitable solvent (e.g. a ketone, such as acetone, methyl ethyl ketone or methyl isobutyl ketone, an ether, such as diethyl ether, tetrahydrofuran or dioxane, a chlorinated hydrocarbon, such as methylene chloride or chloroform, or a low molecular weight aliphatic alcohol such as methanol, ethanol or isopropanol) which contains the desired acid or base, or to which the desired acid or base is then added. The salts are obtained by filtering, reprecipitating, precipitating with a nonsolvent for the addition salt or by evaporating the solvent. Salts obtained can be converted by alkalization or by acidification into the free compounds, which in turn can be converted into salts. In this way, pharmacologically intolerable salts can be converted into pharmacologically tolerable salts.

The salts according to aspect 3 of this invention, such as e.g. salts of (E)-3-[1-(4-dimethylaminomethyl-benzenesulfonyl)-1H-pyrrol-3-yl]-N-hydroxy-acrylamide or (E)-N-hydroxy-3-[1-(5-pyridin-2-yl-thiophene-2-sulfonyl)-1H-pyrrol-3-yl]-acrylamide, respectively, with hydrochloric acid, can be obtained as described by way of example herein, or analogously or similarly thereto.

As one possibility, salts can be prepared by methods known in the art for making acid addition salts of amines, e.g. in the presence of hydrochloric acid in a solution or suspension comprising a suitable organic solvent (e.g. a lower alcohol, such as e.g. methanol, ethanol or isopropanol, a ketone, or an ether including dioxane, tetrahydrofurane, diethylether or tert-butyl methyl ether (TBME)), or mixture of organic solvents, or mixtures thereof with water, or water, with or without heating.

The salts are isolated by crystallization, filtering or by evaporation of the solvent(s) and, if desired, purified by washing or stirring with an appropriate solvent or mixture of solvents or recrystallization from an appropriate recrystallization solvent or mixture of solvents by methods known to one of skill in the art.

Thus, depending on the reaction conditions used, the amount of hydrochloric acid contained in the salts of (E)-3-[1-(4-dimethylaminomethyl-benzenesulfonyl)-1H-pyrrol-3-yl]-N-hydroxy-acrylamide or

(E)-N-hydroxy-3-[1-(5-pyridin-2-yl-thiophene-2-sulfonyl)-1H-pyrrol-3-yl]-acrylamide, respectively, with hydrochloric acid may lie in the range from about 0.1 to about 1.9 equivalent, more precisely from about 0.3 to about 1.2 equivalent, more precisely from about 0.6 to about 1.2 equivalent, more precisely from about 0.8 to about 1.2 equivalent, more precisely from about 0.9 to about 1.1 equivalent, more precisely about one, more precisely about 1.0 equivalent hydrochloric acid with respect to the free base (E)-3-[1-(4-dimethylaminomethyl-benzenesulfonyl)-1H-pyrrol-3-yl]-N-hydroxy-acrylamide or (E)-N-hydroxy-3-[1-(5-pyridin-2-yl-thiophene-2-sulfonyl)-1H-pyrrol-3-yl]-acrylamide, respectively, determined according to art-known procedures, e.g. titration.

Crystalline hydrochloride salts of (E)-3-[1-(4-dimethylaminomethyl-benzenesulfonyl)-1H-pyrrol-3-yl]-N-hydroxy-acrylamide can be obtained by a process comprising the step of crystallization or recrystallization of any form or mixtures of any forms of (E)-3-[1-(4-dimethylaminomethyl-benzenesulfonyl)-1H-pyrrol-3-yl]-N-hydroxy-acrylamide with hydrochloric acid in a solution comprising organic solvent (e.g. an alcohol like methanol or ethanol, or a ketone like acetone) or mixture of organic solvents, or mixtures thereof with water, or only water.

Polymorphs can be obtained by a number of methods, as known in the art. Such methods include, without being restricted to, solvent (re)crystallization, precipitating with non-solvent, rapid evaporation, slow evaporation, rapid cooling, slow cooling and the like.

The solvates or particularly hydrates of the compounds according to this invention can be prepared in a manner known per se, e.g. in the presence of the appropriate solvent. Hydrates may be obtained from water or from mixtures of water with polar organic solvents (for example alcohols, e.g. methanol, ethanol or isopropanol, or ketones, e.g. acetone).

Suitably, the conversions mentioned in this invention can be carried out analogously or similarly to methods which are familiar per se to the person skilled in the art.

The person skilled in the art knows on the basis of his/her knowledge and on the basis of those synthesis routes, which are shown and described within the description of this invention, how to find other possible synthesis routes for according to this invention. All these other possible synthesis routes are also part of this invention.

The present invention also relates to the intermediates (including their salts, stereoisomers and salts of the stereoisomers), methods and processes, which are disclosed herein and which are useful in synthesizing compounds according to this invention. Thus, the present invention also relates to processes disclosed herein for preparing compounds according to this invention, which processes comprise one or more steps of converting and/or reacting the mentioned intermediates with the appropriate reaction partners under conditions as disclosed herein.

Having described the invention in detail, the scope of the present invention is not limited only to those described characteristics or embodiments. As will be apparent to persons skilled in the art, modifications, analogies, variations, derivations, homologisations and adaptations to the described invention can be made on the base of art-known knowledge and/or, particularly, on the base of the disclosure (e.g. the explicite, implicate or inherent disclosure) of the present invention without departing from the spirit and scope of this invention as defined by the scope of the appended claims.

The following examples serve to illustrate the invention further without restricting it. Likewise, further compounds according to this invention, whose preparation is not explicitly described, can be prepared in an analogous manner or in a manner familiar per se to the person skilled in the art using customary process techniques.

Any or all of the compounds of formula I, which are mentioned as final products in the following examples, as well as their salts are a preferred subject of the present invention.

In addition, any or all of the salts of compounds of formula I, which are mentioned as final products in the following examples, their hydrates as well as the polymorphs of these salts and hydrates are a preferred subject of the present invention.

In further addition, any or all of the polymorphs of the salts of compounds of formula I, which are mentioned as final products in the following examples, as well as their hydrates and mixtures thereof are a preferred subject of the present invention.

In the examples, MS stands for mass spectrum, M for molecular ion, TSP for Thermospray Ionization, ESI for Electrospray Ionization, EI for Electron Ionization, h for hours, min for minutes. Other abbreviations used herein have the meanings customary per se to the person skilled in the art.

## Examples

### Final products

#### 1. (E)-N-Hydroxy-3-[1-(toluene-4-sulfonyl)-1H-pyrrol-3-yl]-acrylamide

0.231 g of (E)-3-[1-(toluene-4-sulfonyl)-1H-pyrrol-3-yl]-acrylic acid (compound A1) are dissolved in 8 ml of dichloromethane at room temperature. Then 50 µl of N,N-dimethylformamide (DMF) are added, 0.275 g of oxalic acid chloride dissolved in 2 ml of dichloromethane are added dropwise and stirred for 1.5 hour. To the solution are added 0.439 g of O-(trimethylsilyl)hydroxylamine and stirred for 15 minutes. Then 20 ml of aqueous hydrochloric acid (1 M strength) are added and extracted with ethyl acetate. The combined organic phase is dried over sodium sulfate. Afterwards it is filtered and evaporated under vacuo. The crude product is purified by silica gel flash chromatography using a gradient of dichloromethane and methanol from 98:2 to 6:4 to yield 0.050 g of the title compound as a white solid.

MS (TSP): 307.0 (MH<sup>+</sup>, 100%)

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): 2.37 (s, 3H); 6.12 (d, J = 15.9 Hz, 1H); 6.54 (m, 1H); 7.25 (m, J = 16.1 Hz, 2H); 7.42 (d, J = 8.1 Hz, 2H); 7.79 (m, 1H); 7.85 (d, J = 8.2 Hz, 2H); 8.96 (bs, exchangeable, 1H); 10.61 (bs, exchangeable, 1H)

#### 2. N-Hydroxy-3-(1-phenylmethanesulfonyl-1H-pyrrol-3-yl)-acrylamide

0.189 g of (E)-3-(1-phenylmethanesulfonyl-1H-pyrrol-3-yl)-N-(tetrahydropyran-2-yloxy)-acrylamide (compound A2) are dissolved in 50 ml of a methanol/water (3/2) solution. Then 0.102 g of the acidic ion exchange resin amberlyst IR15 are added and the mixture is stirred for 91 hours at ambient temperature. The mixture is filtered. The filtrate is evaporated. The residue is crystallized from methanol to give 0.144 g of the title compound as white crystals.

MS (TSP): 307.0 (MH<sup>+</sup>, 100%)

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): 5.00 (s, 2H); 6.11 (d, J = 15.7 Hz, 1H); 6.50 (m, 1H); 6.96 (m, 1H); 7.11 (m, 2H); 7.32 (m, J = 17 Hz, 5H); 8.90 (s, exchangeable, 1H); 10.60 (s, exchangeable, 1H)

#### 3. (E)-3-[1-(Biphenyl-4-sulfonyl)-1H-pyrrol-3-yl]-N-hydroxy-acrylamide

The method used for preparation of this compound is analogous to the method described for compound 2. Starting materials: (E)-3-(1-(biphenyl-4-sulfonyl)-1H-pyrrol-3-yl)-N-(tetrahydro-pyran-2-yloxy)-acrylamide (compound A3) (0.150 g), methanol/water 3/2 (50 ml), amberlyst IR15 (0.300 g). Reaction conditions: room temperature, 34 hours.

Yield: 0.041 g, pale grey crystals

MS (ESI): 381.1 (MH<sup>+</sup>-CH<sub>3</sub>NO<sub>2</sub>, 100%)

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): 6.14 (d, J = 15.8 Hz, 1H); 6.58 (m, 1H); 7.31 (d, J = 15.7 Hz, 1H); 7.43 (m, J = 6.9 Hz, 4H); 7.70 (m, J = 6.6 Hz, 3H); 7.91 (d, J = 8.0 Hz, 2H); 8.02 (d, J = 8.1 Hz, 2H); 8.92 (s, exchangeable, 1H); 10.60 (s, exchangeable, 1H)

#### 4. (E)-3-[1-(4-Dimethylamino-benzenesulfonyl)-1H-pyrrol-3-yl]-N-hydroxy-acrylamide

The method used for preparation of this compound is analogous to the method described for compound 2. Starting materials: (E)-3-[1-(4-dimethylamino-benzene sulfonyl)-1H-pyrrol-3-yl]-N-(tetrahydro-pyran-2-yloxy)-acrylamide (compound A4) (0.200 g), methanol/water 3/2 (50 ml), amberlyst IR15 (0.402 g). Reaction conditions: room temperature, 34 hours.

Yield: 0.098 g, pale red crystals

MS (ESI): 336.0 (MH<sup>+</sup>, 100%)

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): 6.10 (m, *J* = 16.5 Hz, 1H); 6.49 (m, 1H); 6.75 (d, *J* = 9.2 Hz, 2H); 7.24 (m, 2H); 7.64 (m, *J*<sub>1</sub> = 8.6 Hz, *J*<sub>2</sub> = 17.7 Hz, 3H); 8.89 (bs, exchangeable, 1H), 10.59 (bs, exchangeable, 1H)

#### 5. (E)-N-(2-Amino-phenyl)-3-[1-(toluene-4-sulfonyl)-1H-pyrrol-3-yl]-acrylamide

0.116 g of (2-[(E)-3-[1-(toluene-4-sulfonyl)-1-H-pyrrol-3-yl]-allanoylamino]-phenyl)-carbamic acid *tert*-butyl ester (compound A5) are dissolved in 20 ml of dichloromethane at ambient temperature. 2 ml of trifluoroacetic acid (TFA) are added and the solution is stirred for 93 hour. The solvent is evaporated to dryness and to the residue are added 25 ml of water. The water phase is extracted exhaustively with ethyl acetate. Afterwards the combined organic phases are dried over sodium sulfate and filtered. The filtrate is evaporated under vacuo. Then the residue is crystallized from methanol to give 0.050 g of the title compound as white crystals.

MS (ESI): 382.0 (MH<sup>+</sup>, 100%)

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): 2.38 (s, 3H); 4.48 (s, exchangeable, 2H); 6.55 (m, 3H); 6.71 (m, 1H); 6.90 (m, 1H); 7.40 (m, *J* = 8.1 Hz, 5H); 7.70 (m, 1H); 7.89 (d, *J* = 8.3 Hz, 2H); 9.20 (s, exchangeable, 1H)

#### 6. (E)-N-(2-Amino-phenyl)-3-(1-phenylmethanesulfonyl-1H-pyrrol-3-yl)-acrylamide

The method used for preparation of this compound is analogous to the method described for compound 5 with the exception that the product is purified by silica gel flash chromatography using a gradient of dichloromethane/methanol from 99:1 to 95:5.

Starting materials: {2-[(E)-3-[1-(phenylmethanesulfonyl)-1-H-pyrrol-3-yl]-allanoylamino]-phenyl}-carbamic acid *tert*-butyl ester (compound A6) (0.146 g), CH<sub>2</sub>Cl<sub>2</sub> (20 ml), TFA (2 ml). Reaction conditions: room temperature, 65 hours.

Yield: 0.037 g, white crystals

MS (ESI): 382.0 (MH<sup>+</sup>)

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): 4.90 (s, 2H); 5.01 (s, exchangeable, 1H); 6.58 (m, *J* = 5.7 Hz, 3H); 6.74 (m, *J* = 6.7 Hz, 2H); 6.90 (m, 1H); 7.01 (m, 1H); 7.11 (m, *J* = 5.6, 2H); 7.34 (m, *J*<sub>1</sub> = 5.7 Hz, *J*<sub>2</sub> = 6.7 Hz, 5H); 9.25 (s, exchangeable, 1H)

#### 7. (E)-N-(2-Amino-phenyl)-3-[1-(biphenyl-4-sulfonyl)-1H-pyrrol-3-yl]-acrylamide

The method used for preparation of this compound is analogous to the method described for compound 5.

Starting materials: (2-[(E)-3-[1-(biphenyl-4-sulfonyl)-1H-pyrrol-3-yl]-allanoylamino]-phenyl)-carbamic acid *tert*-butyl ester (compound A7) (0.460 mmol), CH<sub>2</sub>Cl<sub>2</sub> (50 ml), TFA (5 ml). Reaction conditions: room temperature, 18 hours.



Yield: 0.061 g, white crystals

MS (ESI): 444.0 (MH<sup>+</sup>)

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): 4.90 (bs, exchangeable, 2H); 6.58 (m,  $J_1 = 51.4$  Hz,  $J_2 = 7.5$  Hz, 3H); 6.71 (m,  $J_1 = 1.4$  Hz,  $J_2 = 6.6$  Hz, 1H); 6.90 (m,  $J_1 = 1.4$  Hz,  $J_2 = 6.6$  Hz, 1H); 7.40 (m,  $J_1 = 7.5$  Hz,  $J_2 = 7.7$  Hz, 6H); 7.78 (m,  $J = 7.7$  Hz, 3H); 7.95 (d,  $J = 8.6$  Hz, 2H); 8.08 (d,  $J = 8.8$  Hz, 2H); 9.23 (s, exchangeable, 1H)

**8. (E)-N-(2-Amino-phenyl)-3-[1-(4-dimethylamino-benzenesulfonyl)-1H-pyrrol-3-yl]-acrylamide**

The method used for preparation of this compound is analogous to the method described for compound 5 with the exception that the product is purified by crystallization from ethyl acetate.

Starting materials: (2-[(E)-3-[1-(4-dimethylamino-benzenesulfonyl)-1H-pyrrol-3-yl]-allanoylamino]-phenyl)-carbamic acid *tert*-butyl ester (compound A8) (0.141 g), CH<sub>2</sub>Cl<sub>2</sub> (10 ml), TFA (1 ml). Reaction conditions: room temperature, 20 hours.

Yield: 0.109 g, pale red crystals

MS (ESI): 411.0 (MH<sup>+</sup>, 100%)

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): 3.00 (s, 6H); 3.97 (s, exchangeable, 2H); 6.79 (m,  $J = 15.4$  Hz, 2H); 6.79 (d,  $J = 9.2$  Hz, 2H); 7.04 (m,  $J_1 = 2.7$  Hz,  $J_2 = 8.7$  Hz,  $J_3 = 15.5$  Hz, 3H); 7.40 (m,  $J_1 = 15.6$  Hz,  $J_2 = 8.6$  Hz, 3H) 7.70 (m,  $J_1 = 2.9$  Hz,  $J_2 = 9.2$  Hz, 3H) 9.74 (s, exchangeable, 1H)

**9. (E)-N-Hydroxy-3-(1-[4-([2-(1H-indol-2-yl)-ethyl]-methyl-amino)-methyl]-benzene sulfonyl]-1H-pyrrol-3-yl)-acrylamide**

81 mg of (E)-3-(1-[4-([2-(1H-indol-2-yl)-ethyl]-methyl-amino)-benzenesulfonyl]-1H-pyrrol-3-yl)-N-(tetrahydropyran-2-yloxy)-acrylamide (compound A9) are dissolved in 5 ml of methanol. After addition of 15 ml of 0.1N hydrochloric acid the mixture is stirred for 21 hour. Then the reaction mixture is evaporated. The residue is washed with ethyl acetate and dried under vacuum at -50°C.

Yield: 55 mg, pale yellow solid

**10. (E)-3-[1-(4-Dimethylaminomethyl-benzenesulfonyl)-1H-pyrrol-3-yl]-N-hydroxy-acrylamide**

Procedure a:

The method used for to preparation of this compound is analogous to the method described for compound 9.

Starting material: (E)-3-[1-(4-Dimethylaminomethyl-benzenesulfonyl)-1H-pyrrol-3-yl]-N-tetrahydropyran-2-yloxy)-acrylamide (compound A10)

Procedure b:

According to preferred procedure, the title compound can be obtained as follows:

704 mg of the compound, which is obtained according to the procedure a described in Example 10, is suspended in 1.8 mL isopropanol and 1.8 mL water. The suspension is heated to reflux until the residue is dissolved. 1.9 mL aqueous sodium hydroxide solution (1 mol/l) is added and the solution is

cooled to 5°C. The crystals are filtered by suction and the residue is dried by vacuum. Offwhite crystals (601 mg) of (E)-3-[1-(4-Dimethylaminomethyl-benzenesulfonyl)-1H-pyrrol-3-yl]-N-hydroxy-acrylamide are obtained.

<sup>1</sup>H-NMR (200 MHz, d6-DMSO):  $\delta$  = 2.13 (s, 6 H, 2 CH<sub>3</sub>), 3.46 (s, 2 H, CH<sub>2</sub>), 6.15 (d, 1 H, J = 16.1 Hz, CH=CH), 6.57 (bs, 1 H, Ar-H), 7.29 (d, 1 H, J = 16.1 Hz, CH=CH), 7.37 (m, 1 H, Ar-H), 7.56 (d, 2 H, J = 8.8 Hz, Ar-H), 7.69 (s, 1 H, Ar-H), 7.93 (d, 2 H, J = 8.8 Hz, Ar-H), 8.93 (bs, 1 H, exchangeable-H), 10.58 (bs, 1 H, exchangeable-H)

**11. (E)-N-Hydroxy-3-[1-(4-[(pyridin-3-ylmethyl)-amino]-methyl)-benzenesulfonyl]-1H-pyrrol-3-yl]-acrylamide**

Starting from compound A11, the method which can be used for the preparation is analogous to the method described for compound 9. The crude product is pure enough for biological testing.

MH<sup>+</sup> = 413.0

**12. (E)-N-Hydroxy-3-[1-(4-[(1H-indol-3-ylmethyl)-amino]-methyl)-benzenesulfonyl]-1H-pyrrol-3-yl]-acrylamide**

Starting from compound A12, the method which can be used for the preparation is analogous to the method described for compound 9. The crude product is pure enough for biological testing.

MH<sup>+</sup> = 449.0

**13. (E)-3-[1-[4-(Benzylamino-methyl)-benzenesulfonyl]-1H-pyrrol-3-yl]-N-hydroxy-acrylamide**

Starting from compound A13, the method which can be used for the preparation is analogous to the method described for compound 9.

MH<sup>+</sup> = 412.1

**14. (E)-N-Hydroxy-3-[1-[4-(isobutylamino-methyl)-benzenesulfonyl]-1H-pyrrol-3-yl]-acrylamide**

Starting from compound A14, the method which can be used for the preparation is analogous to the method described for compound 9.

MH<sup>+</sup> = 378.1

**15. (E)-N-Hydroxy-3-[1-(4-[(1H-indol-5-ylmethyl)-amino]-methyl)-benzenesulfonyl]-1H-pyrrol-3-yl]-acrylamide**

Starting from compound A15, the method which can be used for the preparation is analogous to the method described for compound 9.

MH<sup>+</sup> = 449.1

**16. (E)-N-Hydroxy-3-[1-(4-[(pyridin-4-ylmethyl)-amino]-methyl)-benzenesulfonyl]-1H-pyrrol-3-yl]-acrylamide**

Starting from compound A16, the method which can be used for the preparation is analogous to the method described for compound 9.

MH<sup>+</sup> = 413.1

**17. (E)-3-[1-(4-Aminomethyl-benzenesulfonyl)-1H-pyrrol-3-yl]-N-hydroxy-acrylamide**

Starting from compound B6, the method which can be used for the preparation is analogous to the method described for compound 9. The crude product is purified by washing with methanol. A solid is obtained in 69% yield.

Melting point: 227.0-228.6°C

**18. (E)-N-Hydroxy-3-[1-(4-pyridin-4-yl-benzenesulfonyl)-1H-pyrrol-3-yl]-acrylamide**

Starting from compound A17, the method which can be used for the preparation is analogous to the method described for compound 9. The reaction mixture is partly evaporated and the resulting suspension is filtered. The product is isolated as colorless solid.

Melting point: 219.3-221.4°C

**19. (E)-N-Hydroxy-3-{1-[4-(1H-pyrazol-4-yl)-benzenesulfonyl]-1H-pyrrol-3-yl}-acrylamide**

Starting from compound A18, the method which can be used for the preparation is analogous to the method described for compound 9.

Melting point: 203.8-211.9°C

**20. (E)-N-(2-Amino-phenyl)-3-[1-(4-pyridin-4-yl-benzenesulfonyl)-1H-pyrrol-3-yl]-acrylamide**

Starting from compound A19, the method which can be used for the preparation is analogous to the method described for compound 21.

Melting point: 244.2-246.5°C

**21. (E)-N-(2-Amino-phenyl)-3-[1-(4-pyridin-3-yl-benzenesulfonyl)-1H-pyrrol-3-yl]-acrylamide**

The compound is prepared by treatment of (2-((E)-3-[1-(4-pyridin-3-yl-benzenesulfonyl)-1H-pyrrol-3-yl]-allanoylamino)-phenyl)-carbamic acid *tert*-butyl ester (compound A20) in dioxane with HCl. After the reaction is finished, the product precipitates from the reaction mixture.

Melting point: 199.7-202.3°C

**22. (E)-N-(2-Amino-phenyl)-3-{1-[4-(1H-pyrazol-4-yl)-benzenesulfonyl]-1H-pyrrol-3-yl}-acrylamide**

Starting from compound A21, the method which can be used for the preparation is analogous to the method described for compound 21.

Melting point: 232.3-240.9 °C

**23. (E)-3-[1-(Biphenyl-3-sulfonyl)-1H-pyrrol-3-yl]-N-hydroxy-acrylamide**

Starting from compound A22, the method which can be used for the preparation is analogous to the method described for compound 9.

Melting point: 114-159.4°C Sinter at 83°C

**24. (E)-N-Hydroxy-3-[1-(5-pyridin-2-yl-thiophene-2-sulfonyl)-1H-pyrrol-3-yl]-acrylamide**

Starting from compound A23, the method which can be used for the preparation is analogous to the method described for compound 9. The product crystallizes from the reaction mixture.

Melting point: 181.3-182°C

**25. (E)-N-Hydroxy-3-[1-(4-pyrazol-1-yl-benzenesulfonyl)-1H-pyrrol-3-yl]-acrylamide**

Starting from compound A24, the method which can be used for the preparation is analogous to the method described for compound 9. The crude product is purified by washing with dichloromethane.

Melting point: 160.7-166.6°C

**26. (E)-N-(2-Amino-phenyl)-3-[1-(5-pyridin-2-yl-thiophene-2-sulfonyl)-1H-pyrrol-3-yl]-acrylamide**

Starting from compound A25, the method which can be used for the preparation is analogous to the method described for compound 21. The product is purified by washing the crude product with ethyl acetate.

Melting point: 171.3-174.7°C

**27. (E)-N-Hydroxy-3-[1-(4-morpholin-4-ylmethyl-benzenesulfonyl)-1H-pyrrol-3-yl]-acrylamide**

Starting from compound A26, the method which can be used for the preparation is analogous to the method described for compound 9. The title compound is isolated by freeze-drying methods.

Melting point: 168-170°C

**28. (E)-N-Hydroxy-3-{1-[4-({(2-hydroxy-ethyl)-[2-(1H-indol-2-yl)-ethyl]-amino}-methyl)-benzenesulfonyl]-1H-pyrrol-3-yl}-acrylamide**

Starting from compound A 27, the method which can be used for the preparation is analogous to the method described for compound 9. The reaction mixture is evaporated and the title compound is isolated as an oil.

MH<sup>+</sup> = 509.1

Starting from compound D6, the following compounds may be prepared via synthesis routes which are analogous to the synthesis routes resulting to the Examples 18 to 22.

**29. (E)-N-Hydroxy-3-[1-(3-pyridin-4-yl-benzenesulfonyl)-1H-pyrrol-3-yl]-acrylamide**

**30. (E)-N-(2-Amino-phenyl)-3-[1-(3-pyridin-4-yl-benzenesulfonyl)-1H-pyrrol-3-yl]-acrylamide**

**31. (E)-N-(2-Amino-phenyl)-3-[1-(3-pyridin-3-yl-benzenesulfonyl)-1H-pyrrol-3-yl]-acrylamide**

**32. (E)-N-Hydroxy-3-{1-[3-(1H-pyrazol-4-yl)-benzenesulfonyl]-1H-pyrrol-3-yl}-acrylamide**

**33. (E)-N-(2-Amino-phenyl)-3-{1-[3-(1H-pyrazol-4-yl)-benzenesulfonyl]-1H-pyrrol-3-yl]-acrylamide**

**Salts of (E)-N-hydroxy-3-[1-(5-pyridin-2-yl-thiophene-2-sulfonyl)-1H-pyrrol-3-yl]-acrylamide with hydrochloric acid:**

(E)-N-Hydroxy-3-[1-(5-pyridin-2-yl-thiophene-2-sulfonyl)-1H-pyrrol-3-yl]-acrylamide; compound with about 0.3 equivalent hydrochloric acid with respect to the free base:

200 mg of the compound, which is obtained according to the procedure described in Example 24, is suspended in 7 ml 1 N HCl. 3 drops of methanol are added. The suspension is heated to 80 °C and stirred at RT for 2,5 h. Afterwards the suspension is cooled in an ice-bath. The solid is filtered, washed with 20 ml water and dried overnight on high vacuum. Yellow crystals (200 mg) are obtained with a melting point of 172-175 °C. The compound contains 0.30 eq HCl/mol and 5.0% wt water.

**Salt of (E)-N-hydroxy-3-[1-(5-pyridin-2-yl-thiophene-2-sulfonyl)-1H-pyrrol-3-yl]-acrylamide with hydrochloric acid**

1000 mg (E)-N-hydroxy-3-[1-(5-pyridin-2-yl-thiophene-2-sulfonyl)-1H-pyrrol-3-yl]-acrylamide is suspended in 10 mL hydrochloric acid in isopropanol (5 mol/l). The suspension is stirred for 2 h at room temperature. The solvent is evaporated and the residue is suspended in 10 mL isopropanol. After stirring for 24 h the crystals are filtered and dried in vacuum. Beige crystals (730 mg) are obtained. The compound contains 0.91 eq hydrochloric acid/mol.

<sup>1</sup>H-NMR (200 MHz, d<sub>6</sub>-DMSO): δ = 6.19 (d, 1 H, J = 15.8 Hz, CH=CH), 6.61 (bs, 1 H, Ar-H), 7.25-7.47 (m, 3 H, CH=CH, 2 Ar-H), 7.72 (bs, 1 H, Ar-H), 7.86-8.00 (m, 3 H, 3 Ar-H), 8.08 (d, 1 H, J = 8.1 Hz, Ar-H), 8.58 (d, 1 H, J = 4.6 Hz, Ar-H)

**Salts of (E)-3-[1-(4-Dimethylaminomethyl-benzenesulfonyl)-1H-pyrrol-3-yl]-N-hydroxy-acrylamide with hydrochloric acid:**

Form A polymorph of a hydrochloride salt of (E)-3-[1-(4-Dimethylaminomethyl-benzenesulfonyl)-1H-pyrrol-3-yl]-N-hydroxy-acrylamide:

a.) Form A polymorph with about 1.0 equivalent hydrochloric acid with respect to the free base:

200 mg of the compound, which is obtained according to the procedure described in Example 10, is dissolved in aqueous hydrochloric acid (30ml, 1M) with a drop of methanol by heating. Now it is cooled quickly by means of an ice bath. During the cooling procedure pale pink crystals are formed. The product is filtrated and dried under vacuum.

Melting point: 215-219 °C.

Content of HCl: 0.95 HCl/mol

Yield: 99 mg (pale pink crystals, cube form)

X-ray powder diffraction pattern: characteristic peaks of this compound are substantially summarized in Table A and substantially shown in Fig. Aa given later in this application.

Alternatively:

b.) Form A polymorph with about 0.9 equivalent hydrochloric acid with respect to the free base:

200 mg of the compound, which is obtained according to the procedure as described in Example 10, is dissolved in aqueous hydrochloric acid (30ml, 1M) with a drop of ethanol by heating. Now is added slowly isopropyl ether (15ml). There are formed two phases. This mixture is evaporated at 40 °C. During the evaporation process there are formed slowly crystals. Now the evaporation is stopped and the mixture is cooled to room temperature. The product is filtrated and dried under vacuum.

Melting point: 216-217 °C; Content of HCl: 0.85 HCl/mol; Contains ca. 4.4 % wt water;

Yield: 139 mg (pale yellow crystals, plat form);

X-ray powder diffraction pattern: characteristic peaks of this compound are substantially summarized in Table A and substantially shown in Fig. Ab given later in this application;

Differential Scanning Calorimetry: thermoanalytical properties of this compound are substantially summarized in Table C given later in this application.

Form B polymorph of a hydrochloride salt of (E)-3-[1-(4-Dimethylaminomethyl-benzenesulfonyl)-1H-pyrrol-3-yl]-N-hydroxy-acrylamide:

a.) Form B polymorph with about 1.0 equivalent hydrochloric acid with respect to the free base:

200 mg of the compound, which is obtained according to the procedure as described in Example 10, is dissolved in aqueous hydrochloric acid (30ml, 1M) with a drop of methanol by heating. During cooling overnight to room temperature pale pink crystals are formed. The crystals are filtered and dried under vacuum. Melting point: 224-226 °C; Content of HCl: 0.96 HCl/mol;

Yield: 137 mg (pale pink crystals, split form);

X-ray powder diffraction pattern: characteristic peaks of this compound are substantially summarized in Table B and shown in Fig. B given later in this application;

Differential Scanning Calorimetry: thermoanalytical properties of this compound are substantially summarized in Table D given later in this application.

Further forms of salts of (E)-3-[1-(4-Dimethylaminomethyl-benzenesulfonyl)-1H-pyrrol-3-yl]-N-hydroxy-acrylamide with hydrochloric acid:

Salt of (E)-3-[1-(4-Dimethylaminomethyl-benzenesulfonyl)-1H-pyrrol-3-yl]-N-hydroxy-acrylamide with about 1.0 equivalent hydrochloric acid with respect to the free base:

200 mg of the compound, which is obtained according to the procedure as described in Example 10, is dissolved in hydrochloric acid (20ml, 1N), acetone (5 ml) and methanol (1 ml) by heating. After cooling overnight the solution was evaporated. During evaporation crystals are formed and the evaporation process is stopped. The mixture is cooled overnight to ambient temperature and the resulting crystals are collected by suction and dried in vacuum. Melting point: 217-220 °C.

Content of HCl: 1.02 HCl/mol; Contains 0.82 % wt water;

Yield: 131 mg (pale grey white solids).

- 50 -

Salt of (E)-3-[1-(4-Dimethylaminomethyl-benzenesulfonyl)-1H-pyrrol-3-yl]-N-hydroxy-acrylamide with about 0.3 equivalent hydrochloric acid with respect to the free base:

2,04 g of the compound, which is obtained according to the procedure a described in Example 10, is dissolved in hydrochloric acid (1M) and methanol (1l, ration 1:1). Then the solution is neutralized with sodium hydroxide solution (10N). This solution is lyophylized. The resulting solid is suspended extensively in ca. 100 ml of water. The crystals are collected by suction and dried in vacuum.

Melting point: 217-219 °C.

Content of HCl: 0.33 HCl/mol; Contains 3.9 % wt water;

Yield: 534 mg (white solid).

Salt of (E)-3-[1-(4-Dimethylaminomethyl-benzenesulfonyl)-1H-pyrrol-3-yl]-N-hydroxy-acrylamide with about 0.7 equivalent hydrochloric acid with respect to the free base:

200 mg of the compound, which is obtained according to the procedure a described in Example 10, is dissolved in hydrochloric acid (30ml, 1N) and a drop of ethanol by heating. During cooling to room temperature overnight crystals are obtained. The crystals are collected and dried under vacuum.

Melting point: 219-221 °C; Content of HCl: 0.74 HCl/mol;

Yield: 110 mg (pale pink crystals).

Unless otherwise noted, the aforementioned melting points are determined by heating the solid products in small glass vessels under visual inspection. The heating rate is between 0.5 and 10°C/min in a Büchi melting point apparatus B-540.

**Starting materials****A1 (E)-3-[1-(Toluene-4-sulfonyl)-1H-pyrrol-3-yl]-acrylic acid**

1.60 g of (E)-3-[1-(toluene-4-sulfonyl)-1H-pyrrol-3-yl]-acrylic acid *tert*-butyl ester (compound C1) are dissolved in 70 ml of dichloromethane at ambient temperature. Then 7 ml of trifluoroacetic acid (TFA) are added and stirred for 4 hours. The solvent is evaporated to dryness and to the residue are added 30 ml of water. The water phase is extracted exhaustively with ethyl acetate. Then the organic phase is dried over sodium sulfate. The filtrate is evaporated and dried under vacuo to give 0.951 g of the title compound as a pale grey solid.

MS (TSP): 290.0 (M-H<sup>+</sup>, 100%)

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): 2.36 (s, 3H); 6.20 (d, *J* = 15.9 Hz, 1H); 6.74 (m, *J* = 3.1 Hz, 1H); 7.41 (m, *J*<sub>1</sub> = 3.1 Hz, *J*<sub>2</sub> = 8.2 Hz, *J*<sub>3</sub> = 16.1 Hz, 4H); 7.78 (m, 1H), 7.87 (d, *J* = 8.4 Hz, 2H); 11.80 (bs, exchangeable, 1H)

**A2 (E)-3-(1-Phenylmethanesulfonyl-1H-pyrrol-3-yl)-N-(tetrahydropyran-2-yloxy)-acrylamide**

0.295 g of (E)-3-(1-phenylmethanesulfonyl-1H-pyrrol-3-yl)-acrylic acid (compound B1), 0.152 g of N-hydroxybenzotriazole hydrate (HOBt·H<sub>2</sub>O) and 561 µl of triethylamine are dissolved in 20 ml of N,N-dimethylformamide (DMF) at room temperature. Afterwards it is added 0.601 g of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (EDC·HCl) and stirred for 1 hour at room temperature. Then is added 0.152 g of O-(tetrahydro-2H-pyran-2-yl)-hydroxylamine and stirred for 2 hour. The DMF is evaporated under high vacuo. Water is added and the mixture was extracted with ethyl acetate. The organic phase is dried over sodium sulfate. Then it is filtered and evaporated under vacuo. The crude product is purified by silica gel flash chromatography using a gradient of dichloromethane/methanol from 99:1 to 98:2 to give 0.189 g of the title compound as a pale grey solid.

MS (ESI): 390.9 (MH<sup>+</sup>, 100%)

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): 1.60 (m, 6H); 3.51 (m, 1H); 3.91 (m, 1H); 4.89 (m, 1H); 5.00 (s, 2H); 6.18 (d, *J* = 15.3 Hz, 1H); 6.50 (s, 1H); 6.96 (m, *J* = 5.2 Hz, 1H); 7.10 (m, *J*<sub>1</sub> = 7.3 Hz, *J*<sub>2</sub> = 7.9 Hz, 2H); 7.30 (m, *J*<sub>1</sub> = 5.1 Hz, *J*<sub>2</sub> = 7.3 Hz, *J*<sub>3</sub> = 8.1 Hz, *J*<sub>4</sub> = 8.1 Hz, *J*<sub>5</sub> = 15.2 Hz, 5H); 10.60 (s, exchangeable, 1H); 11.08 (bs, exchangeable, 1H)

**A3 (E)-3-(1-(Biphenyl-4-sulfonyl)-1H-pyrrol-3-yl)-N-(tetrahydro-pyran-2-yloxy)-acrylamide**

The method used for preparation of this compound is analogous to the method described for compound A2 with the exception that the product is purified by crystallization from water and methanol.

Starting materials: (E)-3-[1-(biphenyl-4-sulfonyl)-1H-pyrrol-3-yl]-acrylic acid (compound B2) (0.300 g), HOBt·H<sub>2</sub>O (0.130 g), triethylamine (668 µl), DMF (20 ml), EDC·HCl (0.508 g), O-(tetrahydro-2H-pyran-yl)hydroxylamine (0.089 g). Reaction conditions: room temperature, 1 hour; room temperature, 18 hours.



Yield: 0.345 g, pale grey solid

MS (ESI): 452.8 ( $MH^+$ ); 369.0 ( $MH^+ - C_5H_9O$ , 100%)

$^1H$ -NMR (DMSO- $d_6$ ): 1.61 (m, 6); 3.50 (m, 1H); 3.92 (m, 1H); 4.87 (m, 1H); 6.21 (d,  $J = 14.7$  Hz, 1H); 6.60 (s, 1H); 7.48 (m,  $J = 6.9$  Hz, 5H); 7.72 (m,  $J_1 = 7.0$  Hz,  $J_2 = 14.7$  Hz, 3H); 7.98 (d,  $J = 8.5$  Hz, 2H); 8.06 (d,  $J = 8.6$  Hz, 2H); 11.06 (bs, exchangeable, 1H)

**A4 (E)-3-[1-(4-Dimethylamino-benzenesulfonyl)-1H-pyrrol-3-yl]-N-(tetrahydro-pyran-2-yloxy)-acrylamide**

The method used for preparation of this compound is analogous to the method described for compound A2 with the exception that the product is purified by silica gel flash chromatography using a gradient of dichloromethane and methanol from 99:1 to 98:2.

Starting materials: (E)-3-[1-(4-dimethylamino-benzensulfonyl)-1H-pyrrol-3-yl]-acrylic acid (compound B3) (0.150 g), HOBt·H<sub>2</sub>O (0.072 g), triethylamine (259  $\mu$ l), DMF (10 ml), EDC·HCl (0.269 g), O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (0.049 g). Reaction conditions: room temperature, 1 hour; room temperature, 17 hours.

Yield: 0.187 g, pale red solid

MS (ESI): 419.2 ( $MH^+$ ); 336.0 ( $MH^+ - C_5H_9O$ , 100%)

$^1H$ -NMR (DMSO- $d_6$ ): 1.61 (m, 6); 3.02 (s, 6H); 3.50 (m, 1H); 3.92 (m, 1H); 4.85 (m, 1H); 6.19 (m, 1H); 6.50 (m, 1H); 6.75 (m,  $J = 9.2$  Hz, 2H); 7.31 (m, 2H); 7.64 (m,  $J = 9.2$  Hz, 3H); 11.01 (bs, exchangeable, 1H)

**A5 (2-[(E)-3-[1-(Toluene-4-sulfonyl)-1-H-pyrrol-3-yl]-allanoylamino]-phenyl)-carbamic acid *tert*-butyl ester**

The method used for preparation of this compound is analogous to the method described for compound A2 with the exception that the product is purified by silica gel flash chromatography using a gradient of dichloromethane and methanol from 99:1 to 98:1.

Starting materials: (E)-3-[1-(toluene-4-sulfonyl)-1H-pyrrol-3-yl]-acrylic acid (compound A1) (0.400 g), HOBt·H<sub>2</sub>O (0.285 g), triethylamine (652  $\mu$ l), DMF (25 ml), EDC·HCl (0.698 g), N-BOC-1,2,4-phenylenediamine (0.286 g). Reaction conditions: room temperature, 1 hour; room temperature, 2 hours.

Yield: 0.609 g, pale grey solid

MS (ESI): 481.7 ( $MH^+$ , 100%)

$^1H$ -NMR (DMSO- $d_6$ ): 1.40 (m, 9H); 2.39 (s, 3H); 6.61 (m,  $J_1 = 1.7$  Hz,  $J_2 = 2.2$  Hz,  $J_3 = 5.0$  Hz, 2H); 7.09 (m,  $J_1 = 1.8$  Hz,  $J_2 = 2.3$  Hz, 2H); 7.37 (m,  $J_1 = 2.0$  Hz,  $J_2 = 5.0$  Hz,  $J_3 = 8.0$  Hz, 4H); 7.64 (m, 1H); 7.88 (d,  $J = 8.4$  Hz, 2H); 8.41 (s, exchangeable, 1H); 9.57 (s, exchangeable, 1H)

**A6 {2-[(E)-3-[1-(Phenylmethanesulfonyl)-1-H-pyrrol-3-yl]-allanoylamino]-phenyl}-carbamic acid *tert*-butyl ester**

The method used for preparation of this compound is analogous to the method described for compound A2 with the exception that the product is purified by silica gel flash chromatography using a gradient of dichloromethane and methanol from 99:1 to 95:5.

Starting materials: (E)-3-(1-phenylmethanesulfonyl-1H-pyrrol-3-yl)-acrylic acid (compound B1) (0.180 g), HOBT·H<sub>2</sub>O (0.090 g), triethylamine (295 µl), DMF (10 ml), EDC·HCl (0.315 g), N-BOC-1,2-phenylenediamine (0.081 g). Reaction conditions: room temperature, 1 hour; room temperature, 17 hours.

Yield: 0.218 g, pale grey solid

MS (ESI): 504.0 (MNa<sup>+</sup>, 100%); 481.8 (MH<sup>+</sup>)

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): 1.42 (m, 9H); 5.04 (s, 2H); 6.56 (m, *J*<sub>1</sub> = 2.2 Hz, *J*<sub>2</sub> = 10.2 Hz, 2H); 7.14 (m, *J*<sub>1</sub> = 2.2 Hz, *J*<sub>2</sub> = 5.5 Hz, *J*<sub>3</sub> = 10.1 Hz, 4H); 7.36 (m, *J*<sub>1</sub> = 5.5 Hz, *J*<sub>2</sub> = 7.2 Hz, 4H); 7.52 (m, *J*<sub>1</sub> = 2.2 Hz, *J*<sub>2</sub> = 7.2 Hz, 2H); 8.49 (s, exchangeable, 1H); 9.67 (s, exchangeable, 1H)

**A7 (2-[(E)-3-[1-(Biphenyl-4-sulfonyl)-1H-pyrrol-3-yl]-allanoylamino]-phenyl)-carbamic acid *tert*-butyl ester**

The method used for preparation of this compound is analogous to the method described for compound A2 with the exception that the product is purified by silica gel flash chromatography using a gradient of toluene/ethyl acetate from 99:1 to 9:1.

Starting materials: (E)-3-[1-(biphenyl-4-sulfonyl)-1H-pyrrol-3-yl]-acrylic acid (compound B2) (0.300 g), HOBT·H<sub>2</sub>O (0.130 g), triethylamine (668 µl), DMF (20 ml), EDC·HCl (0.508 g), N-BOC-1,2-phenylenediamine (0.176 g). Reaction conditions: room temperature, 1 hour; room temperature, 17 hours.

Yield: 0.285 g, pale grey solid

MS (ESI): 543.8 (MH<sup>+</sup>); 487.9 (MH<sup>+</sup> - C<sub>4</sub>H<sub>8</sub>); 336.1 (MH<sup>+</sup> - C<sub>11</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub>, 100%)

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): 1.47 (m, 9H); 6.50 (m, *J* = 5.4 Hz, 1H); 6.64 (m, *J* = 7.7 Hz, 2H); 7.10 (m, *J*<sub>1</sub> = 5.4 Hz, *J*<sub>2</sub> = 7.7 Hz, 3H); 7.51 (m, *J*<sub>1</sub> = *J*<sub>2</sub> = *J*<sub>3</sub> = 3.6 Hz, 5H); 7.73 (m, 2H); 7.81 (m, 1H); 7.96 (d, *J* = 8.6 Hz, 2H); 8.08 (d, *J* = 8.6 Hz, 2H); 8.41 (s, exchangeable, 1H); 8.59 (s, exchangeable, 1H)

**A8 (2-[(E)-3-[1-(4-Dimethylamino-benzenesulfonyl)-1H-pyrrol-3-yl]-allanoylamino]-phenyl)-carbamic acid *tert*-butyl ester**

The method used for preparation of this compound is analogous to the method described for compound A2 with the exception that the product is purified by crystallization from ethyl acetate.

Starting materials: (E)-3-[1-(4-dimethylamino-benzenesulfonyl)-1H-pyrrol-3-yl]-acrylic acid (compound B3) (0.150 g), HOBT·H<sub>2</sub>O (0.072 g), triethylamine (259 µl), DMF (10 ml), EDC·HCl (0.269 g), N-BOC-1,2-phenylenediamine (0.049 g). Reaction conditions: room temperature, 1 hour; room temperature, 21 hours.

Yield: 0.142 g, pale red solid

MS (ESI): 510.9 (MH<sup>+</sup>, 100%)

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): 1.42 (m, 9H); 3.00 (s, 6H); 6.51 (m, 2H) 6.79 (d, *J* = 9.2 Hz, 2H); 7.09 (m, *J* = 5.5 Hz, 2H); 7.36 (m, 2H); 7.50 (m, *J* = 5.5 Hz, 2H); 7.70 (m, *J* = 9.2 Hz, 2H); 8.41 (s, exchangeable, 1H); 9.55 (s, exchangeable, 1H)

**A9 (E)-3-(1-[4-((2-(1H-Indol-2-yl)-ethyl)-methyl-amino)-benzenesulfonyl]-1H-pyrrol-3-yl)-N-(tetrahydropyran-2-yloxy)-acrylamide**

825 mg of (E)-3-(1-[4-((2-(1H-indol-2-yl)-ethyl)-methyl-amino)-benzenesulfonyl]-1H-pyrrol-3-yl)-acrylic acid (compound B4), 165 mg of HOBt·H<sub>2</sub>O and 1.24 ml of triethylamine are dissolved in 70 ml of DMF at room temperature. Afterwards it is added 726 mg of EDC·HCl and stirred for 1 hour. Then 140 mg of O-(tetrahydro-2H-pyran-2-yl)-hydroxylamine are added and stirred for 18 hour. The DMF is evaporated under high vacuum. Then water is added to the residue and extracted with ethyl acetate. The organic phase is dried over sodium sulfate and evaporated under vacuum. Then the mixture is evaporated and the crude product is purified by silica gel flash chromatography using a gradient of dichloromethane and methanol 98:2 – 9:1.

Yield: 289 mg, pale red solid

**A10 (E)-3-[1-(4-Dimethylaminomethyl-benzenesulfonyl)-1H-pyrrol-3yl]-N-tetrahydro-pyran-2-yloxy)-acrylamide**

The method used for to preparation of the title compound is analogous to the method described for compound A9.

Starting materials: (E)-3-[1-(4-Dimethylaminometyl-benzenesulfonyl)-1H-pyrrol-yl]-acrylic acid (compound B5) (1.78 g), HOBt·H<sub>2</sub>O (366 mg), triethylamine (2.1 ml), DMF (80 ml), EDC·HCl (1.54 g), O-(tetrahydro-2H-pyran-2-yl)-hydroxylamine (306 mg). Reaction condition: room temperature, 1 hour; room temperature, 48 hours.

Yield: 835 mg, pale yellow solid

**A11 (E)-3-[1-(4-[(Pyridin-3-ylmethyl)-amino]-methyl)-benzenesulfonyl]-1H-pyrrol-3-yl]-N-(tetrahydro-pyran-2-yloxy)-acrylamide**

A mixture of compound B6, sodium triacetoxymethylborohydride, methanol and 3-pyridinecarboxaldehyde is stirred at ambient temperature overnight. The reaction mixture is evaporated and partitioned between dichloromethane and water. The crude product is purified by silica gel flash chromatography. A nearly colorless oil is obtained.

Starting from compound B6 and the appropriate aldehyde the following compounds A12 to A16 can be obtained according to compound A11.

**A12 (E)-3-[1-(4-[(1H-Indol-3-ylmethyl)-amino]-methyl)-benzenesulfonyl]-1H-pyrrol-3-yl]-N-(tetrahydro-pyran-2-yloxy)-acrylamide**

**A13 (E)-3-{1-[4-(Benzylamino-methyl)-benzenesulfonyl]-1H-pyrrol-3-yl}-N-(tetrahydro-pyran-2-yloxy)-acrylamide**

**A14 (E)-3-{1-[4-(Isobutylamino-methyl)-benzenesulfonyl]-1H-pyrrol-3-yl}-N-(tetrahydro-pyran-2-yloxy)-acrylamide**

**A15 (E)-3-[1-(4-{[(1H-Indol-5-ylmethyl)-amino]-methyl}-benzenesulfonyl)-1H-pyrrol-3-yl]-N-(tetrahydro-pyran-2-yloxy)-acrylamide**

**A16 (E)-3-[1-(4-{[(Pyridin-4-ylmethyl)-amino]-methyl}-benzenesulfonyl)-1H-pyrrol-3-yl]-N-(tetrahydro-pyran-2-yloxy)-acrylamide**

**A17 (E)-3-[1-(4-Pyridin-4-ylphenylsulfonyl)-1H-pyrrol-3-yl]-N-(tetrahydropyran-2-yloxy)-acrylamide**

Starting from compound B7 the title compound can be obtained according to compound A2.

**A18 (E)-3-{1-[4-(1H-Pyrazol-4-yl)-phenylsulfonyl]-1H-pyrrol-3-yl}-N-(tetrahydropyran-2-yloxy)-acrylamide**

Starting from compound B8 the title compound can be obtained according to compound A2.

**A19 [2-((E)-3-{1-[4-Pyridin-4-yl-benzenesulfonyl]-1H-pyrrol-3-yl}-allanoylamino)-phenyl]-carbamic acid tert-butyl ester**

Starting from compound B7 the title compound can be obtained according to compound A5.

**A20 [2-((E)-3-{1-[4-Pyridin-3-yl-benzenesulfonyl]-1H-pyrrol-3-yl}-allanoylamino)-phenyl]-carbamic acid tert-butyl ester**

Starting from compound B9 the title compound can be obtained according to compound A5.

**A21 [2-((E)-3-{1-[4-(1H-Pyrazol-4-yl)-benzenesulfonyl]-1H-pyrrol-3-yl}-allanoylamino)-phenyl]-carbamic acid tert-butyl ester**

Starting from compound B8 the title compound can be obtained according to compound A5.

**A22 (E)-3-(1-(Biphenyl-3-sulfonyl)-1H-pyrrol-3-yl)-N-(tetrahydro-pyran-2-yloxy)-acrylamide**

Starting from compound B10 the title compound can be obtained according to compound A2.

**A23 (E)-3-(1-(5-Pyridin-2-yl-thiophene-2-sulfonyl)-1H-pyrrol-3-yl)-N-(tetrahydro-pyran-2-yloxy)-acrylamide**

Starting from compound B11 the title compound can be obtained according to compound A2.

**A24 (E)-3-(1-(4-Pyrazol-1-yl-benzenesulfonyl)-1H-pyrrol-3-yl)-N-(tetrahydro-pyran-2-yloxy)-acrylamide**

Starting from compound B12 the title compound can be obtained according to compound A2.

**A25 (2-((E)-3-[1-(5-Pyridin-2-yl-thiophene-2-yl-sulfonyl)-1H-pyrrol-3-yl]-allanoylamino)-phenyl)-carbamic acid tert-butyl ester**

Starting from compound B11 the title compound can be obtained according to compound A5.

**A26 (E)-3-{1-[4-(Morpholin-4-yl-methyl)-benzenesulfonyl]-1H-pyrrol-3-yl}-N-tetrahydro-pyran-2-yloxy)-acrylamide**

Starting from compound B13 the title compound can be obtained according to compound A2.

**A27 (E)-3-{1-[4-({[2-hydroxy-ethyl]-[2-(1H-indol-3-yl)-ethyl]-amino}-methyl)-benzenesulfonyl]-1H-pyrrol-3-yl}-N-(tetrahydro-pyran-2-yloxy)-acrylamide**

(E)-3-{1-[4-({[2-(tert-Butyl-dimethyl-silanyloxy)-ethyl]-[2-(1H-indol-3-yl)-ethyl]-amino}-methyl)-benzenesulfonyl]-1H-pyrrol-3-yl}-N-(tetrahydro-pyran-2-yloxy)-acrylamide (compound B 14) (120 mg, 0.169 mmol) is dissolved in THF (20 ml). Then it is added tetrabutylammonium fluoride (203  $\mu$ l, 0.203, 1M in THF) and triethylamine (47  $\mu$ l, 0.338 mmol) and the mixture is stirred for 17 hours. After addition of water (50 ml) and extraction with ethyl acetate the organic phase is dried over sodium sulfate, filtrated and evaporated. The crude product is purified by a silica gel flash chromatography using dichloromethane-methanol eluent.

**B1 (E)-3-(1-Phenylmethanesulfonyl-1H-pyrrol-3-yl)-acrylic acid**

The method used for preparation of this compound is analogous to the method described for compound A1 with the exception that the product is isolated by crystallization from a mixture of acetone (29.7 g), water (10.8 g) and HCl ( $C_{\text{HCl}}=1$  mol/l, 5.3 g).

Starting materials: (E)-3-(1-phenylmethanesulfonyl-1H-pyrrol-3-yl)-acrylic acid *tert*-butylester (compound C2) (1.45g),  $\text{CH}_2\text{Cl}_2$  (80 ml), TFA (8 ml). Reaction conditions: room temperature, 2 hours.

Yield: 0.660 g, pale grey crystals

MS (TSP): 289.9(M-H<sup>+</sup>, 100%)

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): 5.00 (s, 2H); 6.21 (d,  $J = 15.9$  Hz, 1H); 6.72 (m,  $J_1 = 1.9$  Hz,  $J_2 = 3.4$  Hz, 1H); 7.01 (m,  $J = 5.3$ , 1H); 7.10 (m,  $J = 1.6$  Hz, 2H); 7.31 (m, 7.41 (m,  $J_1 = 1.6$  Hz,  $J_2 = 1.9$  Hz,  $J_3 = 3.4$  Hz,  $J_4 = 5.3$  Hz,  $J_5 = 16.1$  Hz, 4H)

**B2 (E)-3-[1-(Biphenyl-4-sulfonyl)-1H-pyrrol-3-yl]-acrylic acid**

The method used for preparation of this compound is analogous to the method described for compound A1.

Starting materials: (E)-3-[1-(biphenyl-4-sulfonyl)-1H-pyrrol-3-yl]-acrylic acid *tert*-butyl ester (compound C3) (1.05 g),  $\text{CH}_2\text{Cl}_2$  (100 ml), TFA (10 ml). Reaction conditions: room temperature, 21 hours.

Yield: 0.710 g, pale yellow solid

MS (ESI): 728.7 (2MNa<sup>+</sup>, 100%); 354.1 (MH<sup>+</sup>)

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): 6.29 (d, *J* = 16.0 Hz, 1H); 6.81 (m, *J*<sub>1</sub> = 1.2 Hz, *J*<sub>2</sub> = 1.8 Hz, *J*<sub>3</sub> = 3.0 Hz, 1H); 7.49 (m, *J*<sub>1</sub> = 3 Hz, *J*<sub>2</sub> = 7.7 Hz, *J*<sub>0</sub> = 16.0 Hz, 5H); 7.75 (m, *J*<sub>1</sub> = 1.3 Hz, *J*<sub>2</sub> = 1.8 Hz, *J*<sub>3</sub> = 7.7 Hz, 2H); 7.85 (s, 1H); 7.95 (d, *J* = 8.6 Hz, 2H); 8.09 (d, *J* = 8.6 Hz, 2H); 12.17 (bs, exchangeable, 1H)

**B3 (E)-3-[1-(4-Dimethylamino-benzensulfonyl)-1H-pyrrol-3-yl]-acrylic acid**

The method used for preparation of this compound is analogous to the method described for compound A1.

Starting materials: (E)-3-[1-(4-dimethylamino-benzensulfonyl)-1H-pyrrol-3-yl]-acrylic acid *tert*-butyl ester (compound C4) (0.801 g), CH<sub>2</sub>Cl<sub>2</sub> (100 ml), TFA (10 ml). Reaction conditions: room temperature, 16 hours.

Yield: 0.550 g, pale red solid

MS (ESI): 662.7 (2MNa<sup>+</sup>, 100%); 321.0 (MH<sup>+</sup>)

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): 2.98 (s, 6H); 6.16 (d, *J* = 15.8 Hz, 1H); 6.68 (m, *J* = 3.2 Hz, 1H); 6.75 (m, *J* = 9.2 Hz, 2H); 7.29 (m, *J* = 2.9 Hz, 1H); 7.43 (d, *J* = 15.9 Hz, 1H); 7.70 (m, *J* = 9.1 Hz, 3H); 12.11 (bs, exchangeable, 1H)

**B4 (E)-3-(1-[4-((2-(1H-indol-2-yl)-ethyl)-methyl-amino)-benzenesulfonyl]-1H-pyrrol-3-yl)-acrylic acid**

1.01 g of (E)-3-(1-[4-((2-(1H-indol-2-yl)-ethyl)-methyl-amino)-benzenesulfonyl]-1H-pyrrol-3-yl)-acrylic acid *tert*-butyl ester (compound C5) are dissolved in 100 ml of dichloromethane and stirred for 5 minutes. It is added 10 ml of TFA and the mixture stirred for 19 hour. The solution is evaporated under vacuum. Then is added toluene to the residue (small amount to purify the TFA salt) and evaporated under vacuum.

Yield: 1.32 g, Pale brown solid

**B5 (E)-3-[1-(4-Dimethylaminomethyl-benzenesulfonyl)-1H-pyrrol-yl]-acrylic acid**

The method used for to preparation of this compound is analogous to the method described for compound B4.

Starting materials: (E)-3-[1-(4-Dimethylaminomethyl-benzenesulfonyl)-1H-pyrrol-yl]-acrylic acid *tert*-butyl ester (compound C6) (2.13 g), TFA (10 ml); 24 hour.

Yield: 3.21 g (with 3 TFA salt), pale brown solid

**B6 (E)-3-[1-(4-Aminomethyl-benzenesulfonyl)-1H-pyrrol-3-yl]-N-(tetrahydro-pyran-2-yloxy)-acrylamide**

To a mixture of 1g of compound C7 and 50 ml ethanol is added 0.57 ml hydrazine hydrate (80%). The mixture is refluxed for 2.5 h. Afterwards, the reaction mixture is cooled to ambient temperature and the resulting white suspension is filtered. The product in the filtrate is purified by silica gel flash chromatography.

**B7 (E)-3-[1-(4-Pyridin-4-ylphenylsulfonyl)-1H-pyrrol-3-yl]-acrylic acid**

Starting from compound C8 the title compound can be obtained according to compound A1.

**B8 (E)-3-{1-[4-(1H-Pyrazol-4-yl)-phenylsulfonyl]-1H-pyrrol-3-yl}-acrylic acid**

Starting from compound C9 the title compound can be obtained according to compound A1.

**B9 (E)-3-[1-(4-Pyridin-3-ylphenylsulfonyl)-1H-pyrrol-3-yl]-acrylic acid**

Starting from compound C10 the title compound can be obtained according to compound A1.

**B10 (E)-3-(1-(Biphenyl-3-sulfonyl)-1H-pyrrol-3-yl)-acrylic acid**

Starting from compound C11 the title compound can be obtained according to compound A1.

**B11 (E)-3-(1-(5-Pyridin-2-yl-thiophene-2-sulfonyl)-1H-pyrrol-3-yl)-acrylic acid**

Starting from compound C12 the title compound can be obtained according to compound A1.

**B12 (E)-3-(1-(4-Pyrazol-1-yl-benzenesulfonyl)-1H-pyrrol-3-yl)-acrylic acid**

Starting from compound C13 the title compound can be obtained according to compound A1.

**B13 (E)-3-{1-[4-(Morpholin-4-yl-methyl)-benzenesulfonyl]-1H-pyrrol-3-yl}-acrylic acid**

Starting from compound C14 the title compound can be obtained according to compound A1.

**B14 (E)-3-{1-[4-({2-( tert-Butyl-dimethyl-silanyloxy)-ethyl}-[2-(1H-indol-3-yl)-ethyl]-amino)-methyl]-benzenesulfonyl]-1H-pyrrol-3-yl}-N-(tetrahydro-pyran-2-yloxy)-acrylamide**

(E)-3-{1-[4-({2-( tert-Butyl-dimethyl-silanyloxy)-ethyl}-[2-(1H-indol-3-yl)-ethyl]-amino)-methyl]-benzenesulfonyl]-1H-pyrrol-3-yl}-acrylic acid (compound C15) (1.15 g, 1.16 mmol), HOBT·H<sub>2</sub>O (171 mg, 1.16 mmol) and triethylamine (2 ml) is dissolved in DMF (100 ml) at room temperature. After addition of EDC·HCl (786 mg, 3.48 mmol) the mixture is stirred for 1.5 hours. Then it is added O-(tetrahydro-2H-pyran-2-yl)-hydroxylamine (136 mg, 1.16 mmol) and stirred for 17 hours. After evaporation and addition of 200ml water the mixture is extracted with ethyl acetate. The organic phase is dried over sodium sulfate. Then it is filtrated and evaporated. The crude product is purified by a silica gel flash chromatography using dichloromethane- methanol eluent.

**C1 (E)-3-[1-(Toluene-4-sulfonyl)-1H-pyrrol-3-yl]-acrylic acid *tert*-butyl ester**

0.230 g of sodium hydride (60%) is suspended in 6 ml of tetrahydrofurane under nitrogen at -30°C. 1.01 g of (E)-3-(1H-pyrrol-3-yl)acrylic acid *tert*-butyl ester (compound D1) are added to the suspension and warmed slowly to room temperature and stirred for 30 minutes. Afterwards it is recooled to -30°C and 1.19 g of p-toluenesulfonylchloride are added and stirred for 2.5 hours. The suspension is warmed slowly at room temperature and 40 ml of saturated aqueous sodium chloride solution are added. The mixture is extracted with ethyl acetate. The combined organic phase is dried over sodium sulfate



(Na<sub>2</sub>SO<sub>4</sub>). Afterwards it is filtered and evaporated under vacuo. The crude product is purified by silica gel flash chromatography using a gradient of hexane-ethyl acetate from 9:1 to 1:1 to give 1.60 g of the title compound as a pale yellow solid.

MS (ESI): 347.6 (MH<sup>+</sup>); 291.9 (MH<sup>+</sup> -C<sub>4</sub>H<sub>9</sub>, 100%)

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): 1.43 (s, 9H); 2.37 (s, 3H); 6.21 (d, *J* = 15.9 Hz, 1H); 6.74 (m, *J* = 3.1 Hz, 1H); 7.40 (m, *J*<sub>1</sub> = 15.9 Hz, *J*<sub>2</sub> = 12.7 Hz, *J*<sub>3</sub> = 3.2 Hz, 4H); 7.82 (m, *J* = 12.6 Hz, 3H)

## **C2 (E)-3-(1-Phenylmethansulfonyl-1H-pyrrol-3-yl)-acrylic acid *tert*-butylester**

The method used for preparation of this compound is analogous to the method described for compound C1 with the exception that the product is purified by silica gel flash chromatography using gradient of hexane/ethyl acetate from 8:1 to 5:1.

Starting materials: sodium hydride 60% (0.240 g), (E)-3-(1H-pyrrol-3-yl)-acrylic acid *tert*-butyl ester (compound D1) (1.01 g), α-toluenesulfonylchloride (1.19 g). Reaction conditions: -30°C, 30 min; -30°C, 2.5 hours.

Yield: 1.45 g, pale yellow solid

MS (TSP): 346.3 (M-H<sup>+</sup>, 100%)

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): 1.47 (s, 9H); 5.00 (s, 2H); 6.21 (d, *J* = 15.8 Hz, 1H); 6.72 (m, *J*<sub>1</sub> = 1.8 Hz, *J*<sub>2</sub> = 3.3 Hz, 1H); 6.98 (m, *J* = 5.3, 1H); 7.09 (m, *J*<sub>1</sub> = 2.1 Hz, *J*<sub>2</sub> = 7.8 Hz, 2H); 7.31 (m, *J*<sub>1</sub> = 1.9 Hz, *J*<sub>2</sub> = 3.5 Hz, *J*<sub>3</sub> = 5.4 Hz, *J*<sub>4</sub> = 7.7 Hz, *J*<sub>5</sub> = 15.7 Hz, 5H)

## **C3 (E)-3-[1-(Biphenyl-4-sulfonyl)-1H-pyrrol-3-yl]-acrylic acid *tert*-butyl ester**

The method used for preparation of this compound is analogous to the method described for compound C1 with the exception that the product is purified by silica gel flash chromatography using a gradient of petroleum ether/diethylether from 7:1 to 1:1.

Starting materials: sodium hydride 60% (0.207 g), (E)-3-(1H-pyrrol-3-yl)-acrylic acid *tert*-butyl ester (compound D1) (0.531 g), 4-biphenylsulphonylchloride (0.834 g). Reaction conditions: -30°C, 10 min; -30°C, 30 min.

Yield: 1.05 g, pale yellow solid

MS (ESI): 354.0 (MH<sup>+</sup> -C<sub>4</sub>H<sub>9</sub>, 100%)

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): 1.45 (s, 9H); 6.26 (d, *J* = 15.9 Hz, 1H); 6.80 (m, *J* = 1.7 Hz, 1H); 7.47 (m, *J* = 15.7 Hz, 5H); 7.72 (m, *J* = 1.8 Hz, 2H); 7.87 (m, 1H), 7.92 (d, *J* = 8.7 Hz, 2H); 8.09 (d, *J* = 8.6 Hz, 2H)

## **C4 (E)-3-[1-(4-Dimethylamino-benzensulfonyl)-1H-pyrrol-3-yl]-acrylic acid *tert*-butyl ester**

The method used for preparation of this compound is analogous to the method described for compound C1 with the exception that the product is purified by silica gel flash chromatography using a gradient of petroleum ether/diethylether from 7:1 to 1:1.

Starting materials: sodium hydride 60% (0.031 g), (E)-3-(1H-pyrrol-3-yl)-acrylic acid *tert*-butyl ester (compound D1) (0.100 g), 4-dimethylamino-benzenesulfonyl chloride (0.145 g). Reaction conditions: -30°C, 45 min; -30°C, 2.5 hours.

Yield: 0.160 g, pale red solid



MS (ESI): 376.8 ( $MH^+$ ); 321.0 ( $MH^+ - C_4H_9$ , 100%)

$^1H$ -NMR (DMSO- $d_6$ ): 1.42 (s, 9H); 3.00 (s, 6H); 6.19 (d,  $J = 15.8$  Hz, 1H); 6.72 (m,  $J = 9.2$  Hz, 3H); 7.25 (m, 1H); 7.37 (d,  $J = 15.8$  Hz, 1H); 7.69 (m,  $J = 9.1$  Hz, 3H)

**C5 (E)-3-(1-[4-((2-(1H-Indol-2-yl)-ethyl)-methyl-amino)-benzenesulfonyl]-1H-pyrrol-3-yl)-acrylic acid *tert*-butyl ester**

1.50 g of (E)-3-[1-(4-bromomethyl-benzenesulfonyl)-1H-pyrrol-3-yl]-acrylic acid *tert*-butyl ester (compound D2) are dissolved in 70 ml of ethanol at room temperature. After addition of 0.486 ml of triethylamine and 696 mg of omega-methyltryptamine it is stirred for 21 hour. Then the solution is evaporated under vacuum. The crude product is purified by silica gel flash chromatography using a gradient of hexane and ethyl acetate from 5:1 - 2:1.

Yield: 1.08 g, pale yellow solid

**C6 (E)-3-[1-(4-Dimethylaminomethyl-benzenesulfonyl)-1H-pyrrol-yl]-acrylic acid *tert*-butyl ester**

The method used for to preparation of this compound is analogous to the method described for compound C5 with the exception that the product was crystallized in ethanol.

Starting materials: (E)-3-[1-(4-Bromomethyl-benzenesulfonyl)-1H-pyrrol-3-yl]-acrylic acid *tert*-butyl ester (compound D2) (3.94g), ethanol (150 ml), dimethylamine (1.89 g)

Yield: 2.19 g, pale yellow solid

**C7 (E)-3-{1-[4-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-benzenesulfonyl]-1H-pyrrol-3-yl}-acrylic acid**

Starting from compound D3 the method which can be used for this preparation is analogous to the method described for the compound B4. The title compound is purified by washing with toluene.

Starting from (E)-3-[1-(4-bromo-benzenesulfonyl)-1H-pyrrol-3-yl]-acrylic acid *tert*-butyl ester (compound D4) and the appropriate boronic acid derivative the following compounds C8 and C9 can be obtained according to compound C10.

**C8 (E)-3-[1-(4-Pyridin-4-ylphenylsulfonyl)-1H-pyrrol-3-yl]-acrylic acid *tert*-butyl ester**

**C9 (E)-3-{1-[4-(1H-Pyrazol-4-yl)-phenylsulfonyl]-1H-pyrrol-3-yl}-acrylic acid *tert*-butyl ester**

**C10 (E)-3-[1-(4-Pyridin-3-ylphenylsulfonyl)-1H-pyrrol-3-yl]-acrylic acid *tert*-butyl ester**

0.18 g (E)-3-[1-(4-bromo-benzenesulfonyl)-1H-pyrrol-3-yl]-acrylic acid *tert*-butyl ester (compound D4) and 62 mg 3-pyridylboronic acid are dissolved in 10 ml DME. A catalytic amount of bis-(triphenylphosphin-palladium (II)-chloride and 0.6 ml of an aqueous solution of sodium carbonate are

added and the mixture is heated to reflux temperature overnight. The title compound is isolated by means of chromatography.

**C11 (E)-3-[1-(Biphenyl-3-sulfonyl)-1H-pyrrol-3-yl]-acrylic acid *tert*-butyl ester**

Starting from (E)-3-(1H-pyrrol-3-yl)-acrylic acid *tert*-butyl ester (compound D1) and art-known 3-biphenylsulphonylchloride the title compound can be obtained analogously or similarly as described for compound C1.

**C12 (E)-3-[1-(5-Pyridin-2-yl-thiophene-2-sulfonyl)-1H-pyrrol-3-yl]-acrylic acid *tert*-butyl ester**

Starting from (E)-3-(1H-pyrrol-3-yl)-acrylic acid *tert*-butyl ester (compound D1) and art-known 5-pyridin-2-yl-thiophene-2-sulphonylchloride the title compound can be obtained analogously or similarly as described for compound C1.

**C13 (E)-3-[1-(4-Pyrazol-1-yl-benzenesulfonyl)-1H-pyrrol-3-yl]-acrylic acid *tert*-butyl ester**

Starting from (E)-3-(1H-pyrrol-3-yl)-acrylic acid *tert*-butyl ester (compound D1) and art-known 4-pyrazol-1-yl-benzenesulphonylchloride the title compound can be obtained analogously or similarly as described for compound C1.

**C14 (E)-3-{1-[4-(Morpholin-4-yl-methyl)-benzenesulfonyl]-1H-pyrrol-3-yl}-acrylic acid *tert*-butyl ester**

Starting from compound D2 and morpholine the title compound can be obtained analogously as described for compound C5.

**C15 (E)-3-{1-[4-({[2-(*tert*-Butyl-dimethyl-silanyloxy)-ethyl]-[2-(1H-indol-3-yl)-ethyl]-amino}-methyl)-benzenesulfonyl]-1H-pyrrol-3-yl}-acrylic acid**

(E)-3-{3-[4-({[2-(*tert*-Butyl-dimethyl-silanyloxy)-ethyl]-[2-(1H-indol-3-yl)-ethyl]-amino}-methyl)-benzenesulfonyl]-1H-pyrrol-3-yl}-acrylic acid *tert*-butyl ester (compound D5) is dissolved in dichloromethane (50 ml). Then it is added TFA and the mixture is stirred for 26 hours. After evaporation, the residue is washed with toluene.

**D1 (E)-3-(1H-Pyrrol-3-yl)-acrylic acid *tert*-butyl ester**

5.29 g of sodium hydride 60% is suspended in 100 ml of tetrahydrofuran under nitrogen at  $-30^{\circ}\text{C}$ . 27.81 g of *tert*-butyl diphosphono acetate are added to the suspension and warmed slowly to room temperature and stirred for 30 minutes. Afterwards the mixture is re-cooled at  $-30^{\circ}\text{C}$  and it is added 5.24 g of 1H-pyrrol-3-carbaldehyde (compound E1) and stirred at  $-30^{\circ}\text{C}$  for 30 minutes. The suspension is warmed slowly to room temperature and 200 ml of aqueous ammonia solution are added. Then it is extracted with ethyl acetate. The combined organic phase is dried over  $\text{Na}_2\text{SO}_4$ , filtered and evaporated under vacuo. The crude product is purified by silica gel flash chromatography using a gradient of n-hexane-ethyl acetate from 2:1 to 1:1 to give 9.68 g of the title compound as a pale yellow solid.

MS (EI): 193.1 ( $M^+$ ); 137.1 ( $M^+ - C_4H_8$ , 100%)

$^1H$ -NMR (DMSO- $d_6$ ): 1.45 (s, 9H); 5.96 (d,  $J = 15.7$  Hz, 1H); 6.40 (m, 1H); 6.78 (m, 1H); 7.19 (m, 1H); 7.47 (d,  $J = 15.7$  Hz, 1H); 11.11 (bs, exchangeable, 1H)

**D2 (E)-3-[1-(4-Bromomethyl-benzenesulfonyl)-1H-pyrrol-3-yl]-acrylic acid *tert*-butyl ester**

4.25 g of sodium hydride (60% strength) are suspended in 300 ml of THF under nitrogen at  $-30^\circ C$ . 9.78 g of (E)-3-(1H-pyrrol-3-yl)-acrylic acid *tert*-butyl ester (compound D1) are added to the suspension and warmed slowly to room temperature during 55 min. Afterwards it is re-cooled to  $-30^\circ C$  and it is added 13.98 g of 4-(bromomethyl)-benzenesulphonylchloride and stirred for 45 min. Then it is warmed to room temperature and stirred for 2 hour. After cooling to  $0-5^\circ C$  water is added. Then the mixture is extracted with ethyl acetate and the organic phase is dried over sodium sulfate. The organic phase is evaporated under vacuum. The crude product is purified by silica gel flash chromatography using a gradient of hexane and ethyl acetate from 9:1- 7:1.

Yield: 17.21 g, pale yellow solid

**D3 (E)-3-{1-[4-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-benzenesulfonyl]-1H-pyrrol-3-yl}-acrylic acid *tert*-butyl ester**

10g (E)-3-[1-(4-bromomethyl-benzenesulfonyl)-1H-pyrrol-3-yl]-acrylic acid *tert*-butyl ester (compound D2) is dissolved in acetone and 6.5 g potassium phthalimide is added and the mixture is stirred for 17.5 h. The suspension is filtered and the product is purified by crystallization.

**D4 (E)-3-[1-(4-Bromo-benzenesulfonyl)-1H-pyrrol-3-yl]-acrylic acid *tert*-butyl ester**

Starting from compound D1 and 4-bromo-benzenesulfonyl chloride the title compound can be obtained analogously as described for compound D2.

**D5 (E)-3-{1-[4-([2-(*tert*-Butyl-dimethyl-silanyloxy)-ethyl]-[2-(1H-indol-3-yl)-ethyl]-amino)-methyl]-benzenesulfonyl]-1H-pyrrol-3-yl}-acrylic acid *tert*-butyl ester**

[2-(*tert*-Butyl-dimethyl-silanyloxy)-ethyl]-[2-(1H-indol-3-yl)-ethyl]-amine (compound E2) (830 mg, 2.60 mmol) is dissolved in ethanol (200 ml). (E)-3-[1-(4-bromomethyl-benzenesulfonyl)-1H-pyrrol-3-yl]-acrylic acid *tert*-butyl ester (compound D4) (1.01 g, 2.37 mmol) is added and the mixture is stirred for 43 hours and evaporated. The residue is purified by a silica gel flash chromatograph using petrol ether- ether eluent.

**D6 (E)-3-[1-(3-Bromo-benzenesulfonyl)-1H-pyrrol-3-yl]-acrylic acid *tert*-butyl ester**

Starting from compound D1 and 3-bromo-benzenesulfonyl chloride the title compound can be obtained analogously as described for compound D4.

**E1 1H-Pyrrol-3-carbaldehyde**

4.70 g of dimethyl-(1H-pyrrol-3-ylmethylene)-ammonium chlorid (compound F1) are dissolved in 500 ml of 5.0% aqueous sodium hydroxide solution and stirred for 4 hours at ambient temperature.

Afterwards the reaction mixture is extracted exhaustively with  $\text{CH}_2\text{Cl}_2$ . The combined organic phase is dried over  $\text{Na}_2\text{SO}_4$ . Then it is filtered and evaporated under vacuo. The crude product is purified by a silica gel flash chromatography using petroleum ether/diethylether 1:1 eluent to yield 3.01 g of the title compound as a pale yellow solid.

MS (EI): 95.1 ( $\text{M}^+$ , 100%)

$^1\text{H}$ -NMR (DMSO- $d_6$ ): 6.42 (dd,  $J_1 = 1.5$  Hz,  $J_2 = 6.5$  Hz, 1H) ; 6.90 (m, 1H), 7.69 (dd,  $J_1 = 1.5$  Hz,  $J_2 = 6.4$  Hz, 1H) ; 9.68 (s, 1H) ; 11.59 (bs, exchangeable, 1H)

## **E2 [2-(tert-Butyl-dimethyl-silanyloxy)-ethyl]-[2-(1H-indol-3yl)-ethyl]-amine**

Tryptamine (3.34 g, 20.85 mmol) and t-butyl dimethylsilyloxyacetaldehyde (2.44 g, 13.99 mmol) is dissolved in dichloromethane (200 ml) for 10 minutes. The mixture is cooled to 0 °C and it is added sodium triacetoxyborohydride (5.38 g, 25.38 mmol). The mixture is warmed slowly to room temperature and stirred for 18 hours. Then water is added and the mixture is extracted with dichloromethane. The organic phase is dried over sodium sulfate, filtered and evaporated. The crude product is purified by a silica gel flash chromatograph using dichloromethane- methanol eluent.

## **F1 Dimethyl-(1H-pyrrol-3-ylmethylene)-ammonium chlorid**

10.60 g of (chloromethylene)dimethylammonium chloride and 6.25 g of N-(triisopropylsilyl)-pyrrole are suspended in 200 ml of  $\text{CH}_2\text{Cl}_2$  under nitrogen at 0-5°C. The suspension is warmed to 60°C and stirred for 30 minutes. Afterwards the mixture is cooled to ambient temperature. The suspension is filtered and washed with diethylether to give 5.67 g of the title compound as grey solid.

MS (ESI): 123.3 ( $\text{MH}^+$ , 100%)

$^1\text{H}$ -NMR (DMSO- $d_6$ ): 3.55 (s, 3H) ; 3.63 (s, 3H) ; 6.82 (m,  $J_1 = 1.4$  Hz,  $J_2 = 1.5$  Hz,  $J_3 = J_4 = 4.8$  Hz, 1H); 7.22 (dd,  $J_1 = 4.7$  Hz,  $J_2 = 4.9$ , 1H), 8.00 (dd,  $J_1 = 1.6$  Hz,  $J_2 = 1.7$  Hz, 1H) ; 8.78 (s, 1H) ; 12.94 (bs, exchangeable, 1H)

X-ray powder diffraction (XRPD):

The XRPD (X-ray powder diffraction) measurements given herein are performed in transmission, Cu-Kalpha, U = 40kV, I = 30mA

Table A: XRPD pattern of polymorph A comprising the following peaks (relative intensities >10)

2Theta	I (rel)
5.8	15.1
11.5	11.8
15.0	100.0
17.1	49.2
17.4	21.0
17.5	12.0
18.2	10.6
19.9	15.9
20.1	33.9
20.6	27.4
21.3	24.1
21.5	34.4
23.2	14.0
24.1	42.9
25.0	18.6
25.4	42.9
25.8	10.9
26.9	12.3
27.5	25.6
28.5	24.3
29.1	48.1
30.1	11.1
30.2	10.2
30.8	11.5
32.3	13.9

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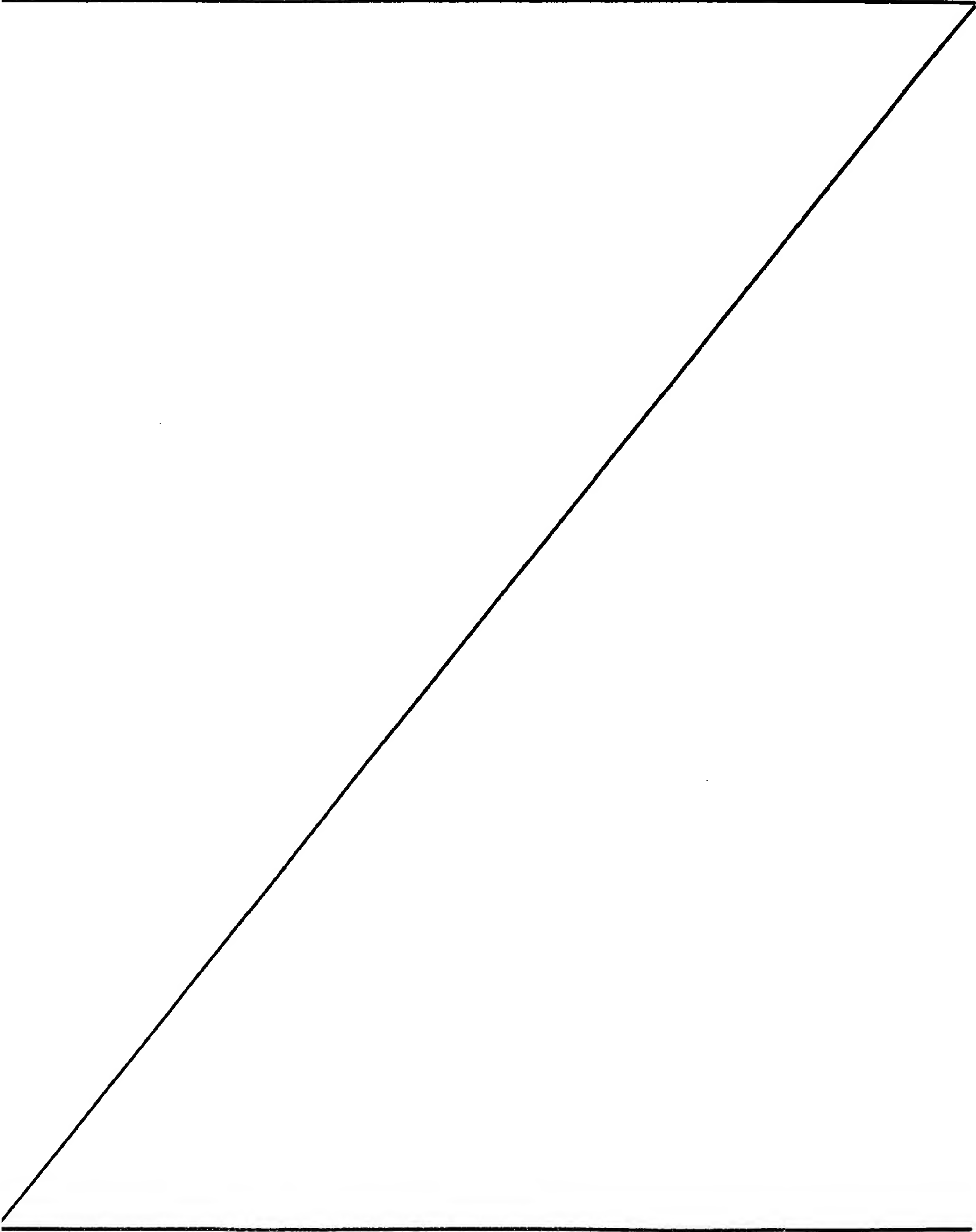


Table B: XRPD pattern of polymorph B comprising the following peaks (relative intensities &gt;10)

2Theta	I (rel)
10.1	11.5
17.0	100.0
17.7	57.7
17.9	61.0
20.3	20.0
20.8	18.6
21.1	47.7
22.7	28.4
23.1	24.5
24.1	11.1
26.2	14.8
26.8	14.2
27.9	14.4
28.4	17.9
28.9	33.9
34.5	12.6

Differential Scanning Calorimetry (DSC):

The DSC scans of the investigated batches are carried out in a temperature range between 30 – 280°C on a dynamical differential scanning calorimeter of TA instruments (DSC Q1000, acquisition software: Q Series Explore Advantage for Q-Series Version 2.1.0.240 Thermal Advantage release 4.1.0, analysis software: Universal Analysis 2000 for Windows 2000/XP v. 4.0C) with dry nitrogen as purge gas (50 mL/min) and a heating rate of 10 K/min. Before performing the DSC sample scans, a T4P calibration (baseline, cell constant, onset slope, cp constant, indium melting point temperature calibration) is carried out.

For the DSC measurements sample amounts between 1.5 and 2.5 mg are accurately weighed into a standard aluminium DSC pan without pin hole (TA instruments, Part 900779.901, T11128) and non-hermetically sealed.

Table C: Polymorph A with about 0.9 eq HCl

Onset-Point / °C		Signal-Maximum / °C		Enthalpy / J /g	
Peak 1	Peak 2	Peak 1	Peak 2	Peak 1	Peak 2
153.0 ± 0.3	215.8 ± 0.7	153.3 ± 0.2	221.3 ± 0.2	62.7 ± 7.1	-355.5 ± 9.4

Table D: Polymorph B

Onset-Point / °C		Signal-Maximum / °C		Enthalpy / J /g	
Peak 1	Peak 2	Peak 1	Peak 2	Peak 1	Peak 2
-	225.9 ± 0.3	-	229.9 ± 0.3	-	-364.8 ± 4.5



**Commercial utility**

The compounds according to this invention have valuable pharmacological properties by inhibiting histone deacetylase activity and function.

Histone deacetylase (HDAC) means an enzyme with an activity towards the  $\epsilon$ -acetyl group of lysine residues within a substrate protein. HDAC substrates are histone H2A, H2B, H3 or H4 proteins and isoforms but substrate proteins different to histones like, but not limited to, heat shock protein 90 (Hsp90), tubulin or the tumor suppressor protein p53 exist. In particular histone deacetylases catalyse the hydrolysis the  $\epsilon$ -acetyl group of lysine residues within these substrate proteins, forming the free amino group of lysine.

Inhibition of histone deacetylase by compounds according to this invention means inhibiting the activity and function of one or more HDAC isoenzymes, in particular isoenzymes selected from the so far known histone deacetylases, namely HDAC 1, 2, 3 and 8 (class I) and HDAC 4, 5, 6, 7, 10 (class II), HDAC 11 as well as the NAD<sup>+</sup> dependent class III (Sir2 homologues). In some preferred embodiment this inhibition is at least about 50%, more preferable at least 75% and still more preferable above 90%. Preferably, this inhibition is specific to a specific histone deacetylase class (eg HDAC class I enzymes), a selection of isoenzymes of highest pathophysiological relevance (eg HDAC1, 2, 3 enzymes) or a single isoenzyme (eg the HDAC 1 enzyme). The term histone deacetylase inhibitor is used to identify a compound capable of interacting with a histone deacetylase and inhibiting its activity, in particular its enzymatic activity. In this context "head group" defines the residues within an histone deacetylase inhibitor responsible for interacting with the active site of the enzyme, eg the Zn<sup>2+</sup> ion.

The inhibition of histone deacetylases is determined in biochemical assays of various formats and sources of enzymatic activity. HDAC activity is used either derived from nuclear or cellular extracts or by heterologous expression of a defined HDAC isoenzymes in E.coli, insect cells or mammalian cells. Since HDAC isoenzymes are active in multiprotein complexes and form homo- and heterodimeres, nuclear extracts derived from human cancer cells, for example the human cervical carcinoma cell line HeLa, are preferred. These nuclear extracts contain class I and class II enzymes, but are enriched in class 1 enzymes. For expression of recombinant HDAC isoenzymes, mammalian expression systems like HEK293 cells are preferred. The HDAC isoenzyme is expressed as a fusion protein with an affinity tag, like the FLAG epitope. By affinity chromatography, the tagged protein is purified alone or in complex with endogenous proteins (eg other HDAC isoenzymes and coactivators / platform proteins). The biochemical assays are well described and well known to persons skilled in the art. As substrates, histone proteins, peptides derived from histone proteins or other HDAC substrates as well as acetylated lysine mimetics are used. One preferred promiscuous HDAC substrate is the tripeptide Ac-NH-GGK(Ac), coupled with the fluorophore 7-aminomethylcoumarin (AMC).

The invention further relates to the use of the compounds according to this invention for inhibiting histone deacetylase activity in cells and tissues, causing hyperacetylation of substrate proteins and as functional consequence for example the induction or repression of gene expression, induction of protein degradation, cell cycle arrest, induction of differentiation and/or induction of apoptosis.

Cellular activity of a histone deacetylase inhibitor means any cellular effect related to histone deacetylase inhibition, in particular protein hyperacetylation, transcriptional repression and activation, induction of apoptosis, differentiation and / or cytotoxicity.

The term "induction of apoptosis" and analogous terms are used to identify a compound which executes programmed cell death in cells contacted with that compound. Apoptosis is defined by complex biochemical events within the contacted cell, such as the activation of cysteine specific proteinases ("caspases") and the fragmentation of chromatin. Induction of apoptosis in cells contacted with the compound might not necessarily coupled with inhibition of cell proliferation or cell differentiation. Preferably, the inhibition of proliferation, induction of differentiation and/or induction of apoptosis is specific to cells with aberrant cell growth.

"Cytotoxicity" in general means arresting proliferation and/or inducing apoptotic cell death in vitro in mammalian cells, in particular human cancer cells.

"Induction of differentiation" is defined as a process of cellular reprogramming leading to a reversible or irreversible cell cycle arrest in G0 and re-expression of a subset of genes typical for a certain specialized normal cell type or tissue (eg re-expression of milk fat proteins and fat in mammary carcinoma cells).

Assays for quantification of cell proliferation, apoptosis or differentiation are well known to experts and state of the art. For example, metabolic activity which is linked to cellular proliferation is quantified using the Alamar Blue / Resazurin assay (O'Brian et al. Eur J Biochem 267, 5421-5426, 2000) and induction of apoptosis is quantified by measurement of chromatin fragmentation with the cell death detection ELISA commercialized by Roche. Examples for cellular assays for the determination of hyperacetylation of HDAC substrates are given by measuring core histone acetylation using specific antibodies by Western blotting, reporter gene assays using respective responsive promoters or promoter elements (eg the p21 promotor or the sp1 site as responsive element) or finally by image analysis again using acetylation specific antibodies for core histone proteins.

Compounds according to this invention can be commercially applicable due to their HDAC inhibitory, anti-proliferative and/or apoptosis inducing activity, which may be beneficial in the therapy of diseases responsive thereto, such as e.g. any of those diseases mentioned herein.

The invention further relates to a method for inhibiting, treating, ameliorating or preventing cellular neoplasia by administration of an effective amount of a compound according to this invention to a mammal, in particular a human in need of such treatment. A "neoplasia" is defined by cells displaying

aberrant cell proliferation and/or survival and/or a block in differentiation. The term neoplasia includes "benign neoplasia" which is described by hyperproliferation of cells, incapable of forming an aggressive, metastasizing tumor in-vivo, and, in contrast, "malignant neoplasia" which is described by cells with multiple cellular and biochemical abnormalities, capable of forming a systemic disease, for example forming tumor metastasis in distant organs.

The compounds according to the present invention are preferably used for the treatment of malignant neoplasia, also described as cancer, characterized by tumor cells finally metastasizing into distinct organs or tissues. Examples of malignant neoplasia treated with the N-sulphonylpyrrole derivatives of the present invention include solid and hematological tumors. Solid tumors are exemplified by tumors of the breast, bladder, bone, brain, central and peripheral nervous system, colon, endocrine glands (e.g. thyroid and adrenal cortex), esophagus, endometrium, germ cells, head and neck, kidney, liver, lung, larynx and hypopharynx, mesothelioma, ovary, pancreas, prostate, rectum, renal, small intestine, soft tissue, testis, stomach, skin, ureter, vagina and vulva. Malignant neoplasia include inherited cancers exemplified by Retinoblastoma and Wilms tumor. In addition, malignant neoplasia include primary tumors in said organs and corresponding secondary tumors in distant organs ("tumor metastases"). Hematological tumors are exemplified by aggressive and indolent forms of leukemia and lymphoma, namely non-Hodgkins disease, chronic and acute myeloid leukemia (CML / AML), acute lymphoblastic leukemia (ALL), Hodgkins disease, multiple myeloma and T-cell lymphoma. Also included are myelodysplastic syndrome, plasma cell neoplasia, paraneoplastic syndromes, cancers of unknown primary site as well as AIDS related malignancies.

It is to be noted that a cancer disease as well as a malignant neoplasia does not necessarily require the formation of metastases in distant organs. Certain tumors exert devastating effects on the primary organ itself through their aggressive growth properties. These can lead to the destruction of the tissue and organ structure finally resulting in failure of the assigned organ function.

Neoplastic cell proliferation might also effect normal cell behaviour and organ function. For example the formation of new blood vessels, a process described as neovascularization, is induced by tumors or tumor metastases. Compounds according to the invention can be commercially applicable for treatment of pathophysiological relevant processes caused by benign or neoplastic cell proliferation, such as but not limited to neovascularization by unphysiological proliferation of vascular endothelial cells.

Drug resistance is of particular importance for the frequent failure of standard cancer therapeutics. This drug resistance is caused by various cellular and molecular mechanisms like overexpression of drug efflux pumps, mutation within the cellular target protein or fusion proteins formed by chromosomal translocations. The commercial applicability of compounds according to the present invention is not limited to 1<sup>st</sup> line treatment of patients. Patients with resistance to cancer chemotherapeutics or target specific anti-cancer drugs can be also amenable for treatment with these

compounds for e.g. 2<sup>nd</sup> or 3<sup>rd</sup> line treatment cycles. A prominent example is given by acute promyelocytic leukemia patients with the PML-RAR $\alpha$  fusion protein, resistant to standard therapy with retinoids. These patients can be resensitized towards retinoids by treatment with HDAC inhibitory drugs like the compounds according to the present invention.

The invention further provides to a method for treating a mammal, in particular a human, bearing a disease different to cellular neoplasia, sensitive to histone deacetylase inhibitor therapy comprising administering to said mammal a pharmacologically active and therapeutically effective and tolerable amount of a compound according to this invention. These non malignant diseases include

- (i) arthropathies and osteopathological conditions or diseases such as rheumatoid arthritis, osteoarthritis, gout, polyarthritis, and psoriatic arthritis,
- (ii) autoimmune diseases like systemic lupus erythematosus and transplant rejection,
- (iii) hyperproliferative diseases such as smooth muscle cell proliferation including vascular proliferative disorders, atherosclerosis and restenosis
- (iv) acute and chronic inflammatory conditions or diseases and dermal conditions such as ulcerative colitis, Chrons disease, allergic rhinitis, allergic dermatitis, cystic fibrosis, chronic obstructive bronchitis and asthma
- (v) endometriosis, uterine fibroids, endometrial hyperplasia and benign prostate hyperplasia
- (vi) cardiac dysfunction
- (vii) inhibiting immunosuppressive conditions like HIV infections
- (viii) neuropathological disorders like Parkinson disease, Alzheimer disease or polyglutamine related disorders
- (ix) pathological conditions amenable to treatment by potentiating of endogenous gene expression as well as enhancing transgene expression in gene therapy.

Compounds according to the present invention may commercially applicable for treatment, prevention or amelioration of the diseases of benign and malignant behavior as described herein, such as, for example, (hyper)proliferative diseases and/or disorders responsive to induction of apoptosis and/or disorders responsive to cell differentiation, e.g. benign or malignant neoplasia, particularly cancer, such as e.g. any of those cancer diseases described above.

In the context of their properties, functions and usabilities mentioned herein, the compounds according to the present invention are expected to be distinguished by valuable and desirable effects related therewith, such as e.g. by low toxicity, superior bioavailability in general (such as e.g. good enteral absorption), superior therapeutic window, absence of significant side effects, and/or further beneficial effects related with their therapeutic and pharmaceutical suitability.

Crystalline compounds according to this invention, e.g. crystalline salts according to this invention, particularly when those compounds are in a specific crystal form (polymorph), are expected to have desirable physicochemical properties that differ from those of any amorphous form and such

properties may beneficially influence the chemical and solid state stability, as well as the chemical and pharmaceutical processing, formulating and mechanical handling on a commercial scale. Thus, those crystalline compounds may be particularly suited for the manufacture of commercially viable and pharmaceutically acceptable drug compositions or dosage forms.

The present invention provides compounds according to this invention in crystalline form.

Also, the present invention provides compounds according to this invention, including their crystalline forms, isolated in purified or substantially pure form, such as e.g. greater than about 50%, more precisely about 60%, more precisely about 70%, more precisely about 80%, more precisely about 90%, more precisely about 95%, more precisely about 97%, more precisely about 99% wt purity as determined by art-known methods.

Also, the present invention provides crystalline compounds according to this invention in substantially pure form, such as e.g. greater than about 50%, more precisely about 60%, more precisely about 70%, more precisely about 80%, more precisely about 90%, more precisely about 95%, more precisely about 97%, more precisely about 99% wt purity as determined by art-known methods, e.g. by XRPD. In this context, the present invention provides crystalline compounds according to this invention, including specific crystalline polymorphs thereof, substantially devoid of amorphous materials, such as e.g. less than about 50%, more precisely 40%, more precisely 30%, more precisely 20%, more precisely 10%, more precisely 5%, more precisely 3%, more precisely 1% wt are amorphous forms of the respective compounds as determined by art-known methods, e.g. by XRPD.

Also, the present invention provides specific crystalline polymorphs of compounds according to this invention in substantially pure form, such as e.g. greater than about 60%, more precisely about 70%, more precisely about 80%, more precisely about 90%, more precisely about 95%, more precisely about 97%, more precisely about 99% wt purity as determined by art-known methods, e.g. by XRPD.

Also, the present invention provides specific crystalline polymorphs of compounds according to this invention in substantially pure form, such as e.g. less than about 40%, more precisely about 30%, more precisely about 20%, more precisely about 10%, more precisely about 5%, more precisely about 3%, more precisely about 1% wt is not said polymorph as determined by art-known methods, e.g. by XRPD.

Accordingly, the present invention provides specific crystalline polymorphs of compounds according to this invention substantially devoid of other crystalline forms.

Also, the present invention provides compounds according to this invention, including their crystalline forms, in a pharmaceutically acceptable form.

Also, the present invention provides compounds according to this invention, including their crystalline forms, in a pharmaceutically acceptable form capable of being milled or in a milled form.

Also, the present invention provides compounds according to this invention, including their crystalline forms, in solid pharmaceutically acceptable forms, particularly solid oral dosage forms, such as tablets and capsules.

The present invention further includes a method for the treatment of mammals, including humans, which are suffering from one of the abovementioned conditions, illnesses, disorders or diseases. The method is characterized in that a pharmacologically active and therapeutically effective and tolerable amount of one or more of the compounds according to this invention, which function by inhibiting histone deacetylases and -in general- by modulating protein acetylation, induce various cellular effects, in particular induction or repression of gene expression, arresting cell proliferation, inducing cell differentiation and/or inducing apoptosis, is administered to the subject in need of such treatment.

The invention further includes a method for treating diseases and/or disorders responsive or sensitive to the inhibition of histone deacetylases, particularly those diseases mentioned above, such as e.g. cellular neoplasia or diseases different to cellular neoplasia as indicated above, in mammals, including humans, suffering therefrom comprising administering to said mammals in need thereof a pharmacologically active and therapeutically effective and tolerable amount of one or more of the compounds according to the present invention.

The present invention further includes a therapeutic method useful to modulate protein acetylation, gene expression, cell proliferation, cell differentiation and/or apoptosis in vivo in diseases mentioned above, in particular cancer, comprising administering to a subject in need of such therapy a pharmacologically active and therapeutically effective and tolerable amount of one or more of the compounds according to this invention, which function by inhibiting histone deacetylases.

The present invention further provides a method for regulating endogenous or heterologous promotor activity by contacting a cell with a compound according to this invention.

The invention further includes a method for treating diseases, particularly those diseases mentioned above, in mammals, including humans, suffering therefrom comprising administering to said mammals in need thereof a therapeutically effective and tolerable amount of one or more of the compounds according to the present invention, optionally, simultaneously, sequentially or separately with one or more further therapeutic agents, such as e.g. those mentioned below.

The invention further relates to the use of the compounds according to the present invention for the production of pharmaceutical compositions which are employed for the treatment and/or prophylaxis of the diseases, disorders, illnesses and/or conditions as mentioned herein.



The invention further relates to the use of the compounds according to the present invention for the production of pharmaceutical compositions which are employed for the treatment and/or prophylaxis of diseases and/or disorders responsive or sensitive to the inhibition of histone deacetylases, particularly those diseases mentioned above, such as e.g. cellular neoplasia or diseases different to cellular neoplasia as indicated above.

The invention further relates to the use of the compounds according to the present invention for the production of pharmaceutical compositions having histone deacetylase inhibitory activity.

The invention further relates to the use of the compounds according to the present invention for the production of pharmaceutical compositions for inhibiting or treating cellular neoplasia, such as e.g. benign or malignant neoplasia, e.g. cancer.

The invention further relates to the use of the compounds according to the present invention for the production of pharmaceutical compositions which can be used for treating, preventing or ameliorating of diseases responsive to arresting aberrant cell growth, such as e.g. (hyper)proliferative diseases of benign or malignant behaviour, such as e.g. any of those diseases mentioned herein, particularly cancer, such as e.g. any of those cancer diseases described herein above.

The invention further relates to the use of the compounds according to the present invention for the production of pharmaceutical compositions which can be used for treating, preventing or ameliorating of disorders responsive to induction of apoptosis, such as e.g. any of those diseases mentioned herein, particularly cancer, such as e.g. any of those cancer diseases described herein above.

The invention further relates to the use of the compounds according to the present invention for the production of pharmaceutical compositions which can be used for treating, preventing or ameliorating of disorders responsive to induction of differentiation, such as e.g. any of those diseases mentioned herein, particularly cancer, such as e.g. any of those cancer diseases described herein above.

The invention further relates to the use of the compounds according to the present invention for the production of pharmaceutical compositions which can be used for treating, preventing or ameliorating of benign or malignant neoplasia, particularly cancer, such as e.g. any of those cancer diseases described herein above.

The invention further relates to the use of the compounds according to the present invention for the production of pharmaceutical compositions for the treatment of a disease different to a cellular neoplasia and sensitive to histone deacetylase inhibitor therapy, such as the non-malignant diseases mentioned before.

The invention further relates to the use of the compounds according to the present invention for the production of pharmaceutical compositions for inhibiting histone deacetylase activity in the treatment of diseases responsive to said inhibition or to the functional consequences thereof.

The invention further relates to a method for treating, preventing or ameliorating the diseases, disorders, illnesses and/or conditions mentioned herein in a mammal, in particular a human patient, comprising administering a pharmacologically active and therapeutically effective and tolerable amount of one or more compounds according to the present invention to said mammal in need thereof.

The invention further relates to the compounds according to this invention for use in the treatment and/or prophylaxis of diseases, especially the diseases mentioned.

The invention further relates to pharmaceutical compositions comprising one or more of the compounds according to this invention and a pharmaceutically acceptable carrier or diluent.

The present invention further relates to pharmaceutical compositions comprising one or more of the compounds according to this invention and pharmaceutically acceptable auxiliaries and/or excipients.

The invention further relates to a combination comprising one or more of the compounds according to this invention and a pharmaceutically acceptable diluent, excipient and/or carrier, e.g. for treating, preventing or ameliorating (hyper)proliferative diseases of benign or malignant behaviour and/or disorders responsive to induction of apoptosis, such as, for example, benign or malignant neoplasia, e.g. cancer, such as e.g. any of those cancer diseases described herein above.

The invention further relates to pharmaceutical compositions according to this invention having histone deacetylases inhibitory activity.

The invention further relates to pharmaceutical compositions according to this invention having apoptosis inducing activity.

The invention further relates to pharmaceutical compositions according to this invention having anti-proliferative activity.

The invention further relates to pharmaceutical compositions according to this invention having cell differentiation inducing activity.

The invention further relates to the use of a pharmaceutical composition comprising one or more of the compounds according to this invention and a pharmaceutically acceptable carrier or diluent in the



manufacture of a pharmaceutical product, such as e.g. a commercial package, for use in the treatment and/or prophylaxis of the diseases as mentioned.

Additionally, the invention relates to an article of manufacture, which comprises packaging material and a pharmaceutical agent contained within said packaging material, wherein the pharmaceutical agent is therapeutically effective for inhibiting the effects of histone deacetylases, ameliorating the symptoms of an histone deacetylase mediated disorder, and wherein the packaging material comprises a label or package insert which indicates that the pharmaceutical agent is useful for preventing or treating histone deacetylase mediated disorders, and wherein said pharmaceutical agent comprises one or more compounds according to the invention. The packaging material, label and package insert otherwise parallel or resemble what is generally regarded as standard packaging material, labels and package inserts for pharmaceuticals having related utilities.

The pharmaceutical compositions according to this invention are prepared by processes which are known per se and familiar to the person skilled in the art. As pharmaceutical compositions, the compounds of the invention (= active compounds) are either employed as such, or preferably in combination with suitable pharmaceutical auxiliaries and/or excipients, e.g. in the form of tablets, coated tablets, capsules, caplets, suppositories, patches (e.g. as TTS), emulsions, suspensions, gels or solutions, the active compound content advantageously being between 0.1 and 95% and where, by the appropriate choice of the auxiliaries and/or excipients, a pharmaceutical administration form (e.g. a delayed release form or an enteric form) exactly suited to the active compound and/or to the desired onset of action can be achieved.

The person skilled in the art is familiar with auxiliaries, vehicles, excipients, diluents, carriers or adjuvants which are suitable for the desired pharmaceutical formulations, preparations or compositions on account of his/her expert knowledge. In addition to solvents, gel formers, ointment bases and other active compound excipients, for example antioxidants, dispersants, emulsifiers, preservatives, solubilizers, colorants, complexing agents or permeation promoters, can be used.

Depending upon the particular disease, to be treated or prevented, additional therapeutic active agents, which are normally administered to treat or prevent that disease, may optionally be coadministered with the compounds according to the present invention. As used herein, additional therapeutic agents that are normally administered to treat or prevent a particular disease are known as appropriate for the disease being treated.

For example, the compounds according to this invention may be combined with standard therapeutic agents or radiation used for treatment of the diseases as mentioned before.

In one particular embodiment the compounds according to this invention may be combined with one or more art-known anti-cancer agents, such as e.g. with one or more art-known chemotherapeutic

and/or target specific anti-cancer agents, e.g. with one or more of those described below, and/or radiation.

Examples of known chemotherapeutic anti-cancer agents frequently used in combination therapy include, but not are limited to (i) alkylating/carbamylating agents such as Cyclophosphamid (Endoxan®), Ifosfamid (Holoxan®), Thiotepa (Thiotepa Lederle®), Melphalan (Alkeran®), or chloroethylnitrosourea (BCNU); (ii) platinum derivatives like cis-platin (Platinex® BMS), oxaliplatin, satraplatin or carboplatin (Cabroplat® BMS); (iii) antimitotic agents / tubulin inhibitors such as vinca alkaloids (vincristine, vinblastine, vinorelbine), taxanes such as Paclitaxel (Taxol®), Docetaxel (Taxotere®) and analogs as well as new formulations and conjugates thereof, epothilones such as Epothilone B (Patupilone®), Azaepothilone (Ixabepilone®) or ZK-EPO, a fully synthetic epothilone B analog; (iv) topoisomerase inhibitors such as anthracyclines (exemplified by Doxorubicin / Adriblastin®), epipodophyllotoxines (exemplified by Etoposide / Etopophos®) and camptothecin and camptothecin analogs (exemplified by Irinotecan / Camptosar® or Topotecan / Hycamtin®); (v) pyrimidine antagonists such as 5-fluorouracil (5-FU), Capecitabine (Xeloda®), Arabinosylcytosine / Cytarabin (Alexan®) or Gemcitabine (Gemzar®); (vi) purin antagonists such as 6-mercaptopurine (Puri-Nethol®), 6-thioguanine or fludarabine (Fludara®) and finally (vii) folic acid antagonists such as methotrexate (Farmitrexat®) or premetrexed (Alimta®).

Examples of target specific anti-cancer drug classes used in experimental or standard cancer therapy include but are not limited to (i) kinase inhibitors such as e.g. Imatinib (Glivec®), ZD-1839 / Gefitinib (Iressa®), Bay43-9006 (Sorafenib, Nexavar®), SU11248 / Sunitinib (Sutent®) or OSI-774 / Erlotinib (Tarceva®), Dasatinib (Sprycel®), Lapatinib (Tykerb®), or, see also below, Vatalanib, Vandetanib (Zactima®) or Pazopanib; (ii) proteasome inhibitors such as PS-341 / Bortezumib (Velcade®); (iii) heat shock protein 90 inhibitors like 17-allylaminogeldanamycin (17-AAG); (iv) vascular targeting agents (VTAs) like combretastin A4 phosphate or AVE8062 / AC7700 and anti-angiogenic drugs like the VEGF antibodies, such as Bevacizumab (Avastin®), or KDR tyrosine kinase inhibitors such as PTK787 / ZK222584 (Vatalanib) or Vandetanib (Zactima®) or Pazopanib; (v) monoclonal antibodies such as Trastuzumab (Herceptin®) or Rituximab (MabThera / Rituxan®) or Alemtuzumab (Campath®) or Tositumomab (Bexxar®) or C225/ Cetuximab (Erbix®) or Avastin (see above) or Panitumumab as well as mutants and conjugates of monoclonal antibodies, e.g. Gemtuzumab ozogamicin (Mylotarg®) or Ibritumomab tiuxetan (Zevalin®), and antibody fragments; (vi) oligonucleotide based therapeutics like G-3139 / Oblimersen (Genasense®); (vii) Toll-like receptor / TLR 9 agonists like Promune®, TLR 7 agonists like Imiquimod (Aldara®) or Isatoribine and analogues thereof, or TLR 7/8 agonists like Resiquimod as well as immunostimulatory RNA as TLR 7/8 agonists; (viii) protease inhibitors (ix) hormonal therapeutics such as anti-estrogens (e.g. Tamoxifen or Raloxifen), anti-androgens (e.g. Flutamide or Casodex), LHRH analogs (e.g. Leuprolide, Goserelin or

Triptorelin) and aromatase inhibitors.

Other known target specific anti-cancer agents which can be used for combination therapy include bleomycin, retinoids such as all-trans retinoic acid (ATRA), DNA methyltransferase inhibitors such as the 2-deoxycytidine derivative Decitabine (Docagen®) and 5-Azacytidine, alanosine, cytokines such as interleukin-2, interferons such as interferon  $\alpha 2$  or interferon- $\gamma$ , death receptor agonists, such as TRAIL, DR4/5 agonistic antibodies, FasL and TNF-R agonists (e.g. TRAIL receptor agonists like mapatumumab or lexatumumab), and finally histone deacetylase inhibitors different to the compounds according to this invention such as SAHA, PXD101, MS275, MGCD0103, Depsipeptide / FK228, NVP-LBH589, NVP-LAQ824, Valproic acid (VPA) and butyrates.

As exemplary anti-cancer agents for use in combination with the compounds according to this invention in the cotherapies mentioned herein any of the following drugs may be mentioned, without being restricted thereto, 5 FU, actinomycin D, ABARELIX, ABCIXIMAB, ACLARUBICIN, ADAPALENE, ALEMTUZUMAB, ALTRETAMINE, AMINOGLUTETHIMIDE, AMIPRILOSE, AMRUBICIN, ANASTROZOLE, ANCITABINE, ARTEMISININ, AZATHIOPRINE, BASILIXIMAB, BENDAMUSTINE, BEVACIZUMAB, BEXXAR, BICALUTAMIDE, BLEOMYCIN, BORTEZOMIB, BROXURIDINE, BUSULFAN, CAMPATH, CAPECITABINE, CARBOPLATIN, CARBOQUONE, CARMUSTINE, CETRORELIX, CHLORAMBUCIL, CHLORMETHINE, CISPLATIN, CLADRIBINE, CLOMIFENE, CYCLOPHOSPHAMIDE, DACARBAZINE, DACLIZUMAB, DACTINOMYCIN, DASATINIB, DAUNORUBICIN, DECITABINE, DESLORELIN, DEXRAZOXANE, DOCETAXEL, DOXIFLURIDINE, DOXORUBICIN, DROLOXIFENE, DROSTANOLONE, EDELFOSINE, EFLORNITHINE, EMITEFUR, EPIRUBICIN, EPITIOSTANOL, EPTAPLATIN, ERBITUX, ERLOTINIB, ESTRAMUSTINE, ETOPOSIDE, EXEMESTANE, FADROZOLE, FINASTERIDE, FLOXURIDINE, FLUCYTOSINE, FLUDARABINE, FLUOROURACIL, FLUTAMIDE, FORMESTANE, FOSCARNET, FOSFESTROL, FOTEMUSTINE, FULVESTRANT, GEFITINIB, GENASENSE, GEMCITABINE, GLIVEC, GOSERELIN, GUSPERIMUS, HERCEPTIN, IDARUBICIN, IDOXURIDINE, IFOSFAMIDE, IMATINIB, IMPROSULFAN, INFlixIMAB, IRINOTECAN, IXABEPILONE, LANREOTIDE, LAPATINIB, LETROZOLE, LEUPRORELIN, LOBAPLATIN, LOMUSTINE, LUPROLIDE, MELPHALAN, MERCAPTOPURINE, METHOTREXATE, METUREDEPA, MIBOPLATIN, MIFEPRISTONE, MILTEFOSINE, MIRIMOSTIM, MITOGUAZONE, MITOLACTOL, MITOMYCIN, MITOXANTRONE, MIZORIBINE, MOTEXAFIN, MYLOTARG, NARTOGRASTIM, NEBAZUMAB, NEDAPLATIN, NILUTAMIDE, NIMUSTINE, OCTREOTIDE, ORMELOXIFENE, OXALIPLATIN, PACLITAXEL, PALIVIZUMAB, PANITUMUMAB, PATUPILONE, PAZOPANIB, PEGASPARGASE, PEGFILGRASTIM, PEMETREXED, PENTETREOTIDE, PENTOSTATIN, PERFOSFAMIDE, PIPOSULFAN, PIRARUBICIN, PLICAMYCIN, PREDNIMUSTINE, PROCARBAZINE, PROPAGERMANIUM, PROSPIDIUM CHLORIDE, RALOXIFEN, RALTITREXED, RANIMUSTINE, RANPIRNASE, RASBURICASE, RAZOXANE, RITUXIMAB, RIFAMPICIN, RITROSULFAN, ROMURTIDE, RUBOXISTAURIN, SARGRAMOSTIM, SATRAPLATIN, SIROLIMUS, SOBUZOXANE, SORAFENIB, SPIROMUSTINE, STREPTOZOCIN, SUNITINIB, TAMOXIFEN, TASONERMIN,

TEGAFUR, TEMOPORFIN, TEMOZOLOMIDE, TENIPOSIDE, TESTOLACTONE, THIOTEPA, THYMALFASIN, TIAMIPRINE, TOPOTECAN, TOREMIFENE, TRAIL, TRASTUZUMAB, TREOSULFAN, TRIAZIQUONE, TRIMETREXATE, TRIPTORELIN, TROFOSFAMIDE, UREDEPA, VALRUBICIN, VATALANIB, VANDETANIB, VERTEPORFIN, VINBLASTINE, VINCRISTINE, VINDESINE, VINORELBINE, VOROZOLE and ZEVALIN.

The anti-cancer agents mentioned herein above as combination partners of the compounds according to this invention are meant to include pharmaceutically acceptable derivatives thereof, such as e.g. their pharmaceutically acceptable salts.

The person skilled in the art is aware on the base of his/her expert knowledge of the kind, total daily dosage(s) and administration form(s) of the additional therapeutic agent(s) coadministered. Said total daily dosage(s) can vary within a wide range.

In practicing the present invention and depending on the details, characteristics or purposes of their uses mentioned above, the compounds according to the present invention may be administered in combination therapy separately, sequentially, simultaneously, concurrently or chronologically staggered (e.g. as combined unit dosage forms, as separate unit dosage forms or a adjacent discrete unit dosage forms, as fixed or non-fixed combinations, as kit-of-parts or as admixtures) with one or more standard therapeutics, in particular art-known chemotherapeutic and/or target specific anti-cancer agents, such as e.g. any of those mentioned above.

Thus, a further aspect of the present invention is a combination or pharmaceutical composition comprising a first active ingredient, which is a compound according to this invention, a second active ingredient, which is an art-known standard therapeutic, in particular art-known chemotherapeutic or target specific anti-cancer agent, such as one of those mentioned above, and optionally a pharmacologically acceptable carrier, diluent and/or excipient for sequential, separate, simultaneous or chronologically staggered use in therapy in any order, e.g. to treat, prevent or ameliorate in a patient diseases responsive to HDAC inhibitor treatment, such as the diseases, disorders or illnesses mentioned, in particular cancer.

In this context, the present invention further relates to a combination comprising a first active ingredient, which is at least one compound according to this invention, and a second active ingredient, which is at least one art-known standard therapeutic, for example an art-known anti-cancer agent, such as e.g. one or more of those mentioned herein above, for separate, sequential, simultaneous, concurrent or chronologically staggered use in therapy, such as e.g. in therapy of any of those diseases mentioned herein.

The term "combination" according to this invention may be present as a fixed combination, a non-fixed combination or a kit-of-parts.

A “fixed combination” is defined as a combination wherein the said first active ingredient and the said second active ingredient are present together in one unit dosage or in a single entity. One example of a “fixed combination” is a pharmaceutical composition wherein the said first active ingredient and the said second active ingredient are present in admixture for simultaneous administration, such as in a formulation. Another example of a “fixed combination” is a pharmaceutical combination wherein the said first active ingredient and the said second active ingredient are present in one unit without being in admixture.

A “kit-of-parts” is defined as a combination wherein the said first active ingredient and the said second active ingredient are present in more than one unit. One example of a “kit-of-parts” is a combination wherein the said first active ingredient and the said second active ingredient are present separately. The components of the kit-of-parts may be administered separately, sequentially, simultaneously, concurrently or chronologically staggered.

The first and second active ingredient of a combination or kit-of-parts according to this invention may be provided as separate formulations (i.e. independently of one another), which are subsequently brought together for simultaneous, sequential, separate or chronologically staggered use in combination therapy; or packaged and presented together as separate components of a combination pack for simultaneous, concurrent, sequential, separate or chronologically staggered use in combination therapy.

The type of pharmaceutical formulation of the first and second active ingredient of a combination or kit-of-parts according to this invention can be similar, i.e. both ingredients are formulated in separate tablets or capsules, or can be different, i.e. suited for different administration forms, such as e.g. one active ingredient is formulated as tablet or capsule and the other is formulated for e.g. intravenous administration.

The amounts of the first and second active ingredients of the combinations, compositions or kits according to this invention may together comprise a therapeutically effective amount for the treatment, prophylaxis or amelioration of a disease responsive or sensitive to the inhibition of histone deacetylases, particularly one of those diseases mentioned herein, e.g. benign or malignant neoplasia, particularly cancer, like any one of those cancer diseases mentioned herein.

A further aspect of the present invention is a combination comprising, in non-fixed form, one or more N-sulphonylpyrrole derivatives according to this invention or the salts thereof, and one or more art-known standard therapeutic, in particular art-known chemotherapeutic or target specific anti-cancer agents, such as those mentioned above, for sequential, separate, simultaneous or chronologically staggered use in therapy in any order, e.g. to treat, prevent or ameliorate in a patient diseases

responsive to HDAC inhibitor treatment, such as the diseases, disorders or illnesses mentioned, in particular cancer. Optionally said combination comprises instructions for its use in therapy.

A further aspect of the present invention is a combined preparation, such as e.g. a kit of parts, comprising a preparation of a first active ingredient, which is a compound according to this invention and a pharmaceutically acceptable carrier or diluent; a preparation of a second active ingredient, which is an art-known therapeutic agent, in particular an anti-cancer agent, such as e.g. one of those mentioned above, and a pharmaceutically acceptable carrier or diluent; and optionally instructions for simultaneous, sequential, separate or chronologically staggered use in therapy, e.g. to treat benign and malignant neoplasia or diseases different to cellular neoplasia responsive or sensitive to the inhibition of histone deacetylases.

A further aspect of the present invention is a kit of parts comprising a dosage unit of a first active ingredient, which is a sulphonylpyrrole derivative mentioned in above or a salt thereof, a dosage unit of a second active ingredient, which is an art-known standard therapeutic, in particular an anti-cancer agent such as e.g. one of those mentioned above, and optionally instructions for simultaneous, sequential or separate use in therapy, e.g. to treat disorders responsive or sensitive to the inhibition of histone deacetylases, such as, for example, benign or malignant neoplasia, e.g. cancer.

A further aspect of the present invention is a pharmaceutical product comprising one or more compounds according to this invention, or one or more pharmaceutical compositions comprising said compounds; and one or more art-known therapeutic agents, in particular art-known anti-cancer agents, or one or more pharmaceutical compositions comprising said therapeutic agents, such as e.g. those mentioned above, for simultaneous, sequential or separate use in therapy, e.g. to treat diseases as mentioned before, in particular cancer. Optionally this pharmaceutical product comprises instructions for use in said therapy.

In this connection, the present invention further relates to combinations, compositions, formulations, preparations or kits according to the present invention having histone deacetylases inhibitory activity.

A further aspect of the present invention is a pharmaceutical composition as unitary dosage form comprising, in admixture, a first active ingredient, which is a N-sulphonylpyrrole derivative according to this invention or a salt thereof, a second active ingredient, which is an art-known standard therapeutic, in particular art-known chemotherapeutic or target specific anti-cancer agent, such as one of those mentioned above, and optionally a pharmacologically acceptable carrier, diluent or excipient.

The present invention further relates to a pharmaceutical composition comprising a first active ingredient, which is at least one compound according to this invention, and a second active ingredient, which is at least one art-known anti-cancer agent, such as e.g. one or more of those mentioned herein above, and, optionally, a pharmaceutically acceptable carrier or diluent,



for separate, sequential, simultaneous, concurrent or chronologically staggered use in therapy, such as e.g. in therapy of diseases responsive or sensitive to the inhibition of histone deacetylases, particularly (hyper)proliferative diseases and/or disorders responsive to induction of apoptosis, such as e.g. any of those diseases mentioned herein, like benign or malignant neoplasia, especially cancer, particularly any of those cancer diseases described above.

The present invention further relates to a combination product comprising

- a.) at least one compound according to this invention formulated with a pharmaceutically acceptable carrier or diluent, and
- b.) at least one art-known anti-cancer agent, such as e.g. one or more of those mentioned herein above, formulated with a pharmaceutically acceptable carrier or diluent.

The present invention further relates to a kit-of-parts comprising a preparation of a first active ingredient, which is a compound according to this invention, and a pharmaceutically acceptable carrier or diluent; a preparation of a second active ingredient, which is an art-known anti-cancer agent, such as one of those mentioned above, and a pharmaceutically acceptable carrier or diluent; for simultaneous, concurrent, sequential, separate or chronologically staggered use in therapy. Optionally, said kit comprises instructions for its use in therapy, e.g. to treat diseases responsive or sensitive to the inhibition of histone deacetylases, such as e.g. cellular neoplasia or diseases different to cellular neoplasia as indicated above, particularly cancer, such as e.g. any of those cancer diseases described above.

The present invention further relates to a combined preparation comprising at least one compound according to this invention and at least one art-known anti-cancer agent for simultaneous, concurrent, sequential or separate administration.

In this connection, the present invention further relates to combinations, compositions, formulations, preparations or kits according to the present invention having histone deacetylases inhibitory activity.

Also in this connection, the present invention further relates to combinations, compositions, formulations, preparation or kits according to the present invention having anti-(hyper)proliferative and/or apoptosis inducing activity.

In addition, the present invention further relates to the use of a composition, combination, formulation, preparation or kit according to this invention in the manufacture of a pharmaceutical product, such as e.g. a commercial package or a medicament, for treating, preventing, or ameliorating diseases responsive or sensitive to the inhibition of histone deacetylases, particularly those diseases mentioned herein, such as e.g. benign or malignant neoplasia, particularly cancer.

The present invention further relates to a commercial package comprising one or more compounds of the present invention together with instructions for simultaneous, sequential or separate use with one or more chemotherapeutic and/or target specific anti-cancer agents, such as e.g. any of those mentioned herein.

The present invention further relates to a commercial package consisting essentially of one or more compounds of the present invention as sole active ingredient together with instructions for simultaneous, sequential or separate use with one or more chemotherapeutic and/or target specific anti-cancer agents, such as e.g. any of those mentioned herein.

The present invention further relates to a commercial package comprising one or more chemotherapeutic and/or target specific anti-cancer agents, such as e.g. any of those mentioned herein, together with instructions for simultaneous, sequential or separate use with one or more compounds according to the present invention.

Furthermore, also an aspect of the present invention is a method for treating diseases and/or disorders responsive or sensitive to the inhibition of histone deacetylases, e.g. (hyper)proliferative diseases and/or disorders responsive to induction of apoptosis, such as e.g. cancer, in combination therapy in a patient comprising administering a pharmacologically active and therapeutically effective and tolerable amount of a pharmaceutical combination, composition, formulation, preparation or kit as described above to said patient in need thereof.

A further aspect of the present invention is a method for treating cotherapeutically diseases responsive or sensitive to inhibiting histone deacetylases, such as e.g. those diseases as mentioned before, particularly cancer, in a patient in need of such treatment comprising administering separately, sequentially, simultaneously, concurrently, fixed or non-fixed a pharmacologically active and therapeutically effective and tolerable amount of one or more of the compounds according to the present invention and a pharmacologically active and therapeutically effective and tolerable amount of one or more art-known therapeutic agents, in particular anti-cancer agents, such as those mentioned above, to said patient.

In further addition, the present invention relates to a method for treating, preventing or ameliorating (hyper)proliferative diseases and/or disorders responsive to induction of apoptosis, such as e.g. benign or malignant neoplasia, e.g. cancer, particularly any of those cancer diseases mentioned herein, in a patient comprising administering separately, simultaneously, concurrently, sequentially or chronologically staggered to said patient in need thereof an amount of a first active compound, which is a compound according to the present invention, and an amount of at least one second active compound, said at least one second active compound being a standard therapeutic agent, particularly at least one art-known anti-cancer agent, such as e.g. one or more of those chemotherapeutic and



target-specific anti-cancer agents mentioned herein, wherein the amounts of the first active compound and said second active compound result in a therapeutic effect.

In yet further addition, the present invention relates to a method for treating, preventing or ameliorating (hyper)proliferative diseases and/or disorders responsive to induction of apoptosis, such as e.g. benign or malignant neoplasia, e.g. cancer, particularly any of those cancer diseases mentioned herein, in a patient comprising administering a combination according to the present invention.

The pharmaceutical compositions, combinations, preparations, formulations, kits, products or packages mentioned above may also include more than one of the compounds according to this invention and/or more than one of the art-known standard therapeutics, in particular anti-cancer agents as mentioned.

In addition, compounds according to the present invention can be used in the pre- or post-surgical treatment of cancer.

In further addition, compounds according to the present invention can be used in combination with radiation therapy, in particular in sensitization of cancer patients towards standard radiation therapy.

The administration of the compounds according to this invention, the combinations and pharmaceutical compositions according to the invention may be performed in any of the generally accepted modes of administration available in the art. Illustrative examples of suitable modes of administration include intravenous, oral, nasal, parenteral, topical, transdermal and rectal delivery. Oral and intravenous delivery are preferred.

For the treatment of dermatoses, the compounds according to the invention are in particular administered in the form of those pharmaceutical compositions which are suitable for topical application. For the production of the pharmaceutical compositions, the compounds of the invention (= active compounds) are preferably mixed with suitable pharmaceutical auxiliaries and further processed to give suitable pharmaceutical formulations. Suitable pharmaceutical formulations are, for example, powders, emulsions, suspensions, sprays, oils, ointments, fatty ointments, creams, pastes, gels or solutions.

The pharmaceutical compositions according to the invention are prepared by processes known per se. The dosage of the compounds according to the invention (=active compounds) is carried out in the order of magnitude customary for histone deacetylases inhibitors. Topical application forms (such as ointments) for the treatment of dermatoses thus contain the active compounds in a concentration of, for example, 0.1-99%. The customary dose in the case of systemic therapy (p.o.) may be between 0.03 and 60 mg/kg per day, (i. v.) may be between 0.03 and 60 mg/kg/h. In another embodiment, the

customary dose in the case of systemic therapy (p.o.) is between 0.3 and 30 mg/kg per day, (i. v.) is between 0.3 and 30 mg/kg/h.

The choice of the optimal dosage regime and duration of medication, particularly the optimal dose and manner of administration of the active compounds necessary in each case can be determined by a person skilled in the art on the basis of his/her expert knowledge.

## **Biological Investigations**

### Isolation of HDAC activity from HeLa cell nuclei:

HDAC activity was isolated from nuclear HeLa extracts according to a method original described by Dignam et al. (Nucl. Acids Res. 11, pp1475, 1983). Briefly, nuclei isolated from HeLa cells (CIL SA, Seneffe, Belgium) were resuspended in buffer C (20mM Hepes pH 7.9, 25% v:v glycerol, 0.42M NaCl, 1.5mM MgCl<sub>2</sub>, 0.2mM EDTA, 0.5mM PefaBloc and 0.5mM DTT) and stirred for 30min on ice. After centrifugation, the supernatant was dialysed against buffer D (40mM Tris HCl pH 7.4, 100mM KCl, 0.2mM EDTA, 0.5mM DTT and 25% v:v glycerol) for 5h at 4°C. After dialysis and centrifugation, the supernatant was stored in aliquots at -80°C and used for Western blot analysis as well as the enzymatic assay as described in the following.

### Isolation of rHDAC1

Human HDAC1 fused with the flag epitope is stably expressed in Hek293 cells. After mass cultivation in DMEM with supplements and 2% fetal calf serum, cells are lysed and flag-HDAC1 purified by M2-agarose affinity chromatography as described (Sigma Art. No. A-2220). Fractions from the purification are analysed by Western blot as well as for enzymatic activity as described below.

### Fluorimetric HDAC activity assay:

The HDAC enzyme activity assay was done as described by Wegener et al. (Chem. & Biol. 10, 61-68, 2003). Briefly 40µl of a 1:100 dilution (= 0.4µl) nuclear HeLa extract (mixture of class I and II HDACs), 29 µl enzyme buffer (15mM Tris HCl pH 8.1, 0.25mM EDTA, 250mM NaCl, 10% v:v glycerol) and 1µl test compound were added to a well of a 96well microtiter plate and reaction started by addition of 30µl substrate (Ac-NH-GGK(Ac)-AMC; final concentration 25µM and final volume 100µl). After incubation for 90min at 30°C, reaction was terminated by the addition of 25µl stop solution (50mM Tris HCl pH 8, 100mM NaCl, 0.5mg/ml trypsin and 2µM TSA). After incubation at room temperature for further 40min, fluorescence was measured using a Wallac Victor 1420 multilabel counter (Ex 355nm, Em 460nm) for quantification of AMC (7-amino-4-methylcoumarin) generated by trypsin cleavage of the deacetylated peptide. For the calculation of IC<sub>50</sub> values the fluorescence in wells without test compound (1% DMSO, negative control) was set as 100% enzymatic activity and the fluorescence in wells with 2µM TSA (positive control) were set at 0% enzymatic activity. The corresponding IC<sub>50</sub> values of the compounds for HDAC inhibitory activity were determined from the concentration-effect curves by means of non-linear regression.

The HDAC inhibitory activity expressed by IC<sub>50</sub> values for selected compounds according to the present invention is shown in the following table 1, in which the numbers of the compounds correspond to the numbers of the examples.

**Table 1: HDAC inhibitory activity (HDAC activity isolated from HeLa nuclear extract)**

Compound	IC <sub>50</sub> (μM)
1 2 3 4 7 8	The IC <sub>50</sub> values of these listed compounds are in the range from 0.0036 to 2.74
9 to 28	The IC <sub>50</sub> values of these listed compounds are in the range from 0.002 to 40

The HDAC1 enzymatic assay is done with slight modifications with recombinant flag-HDAC1 protein isolated from HEK293 cell lysates. About 14ng/well flag-HDAC1 were incubated with 6μM Ac-NH-GGK(Ac)-AMC substrate for 3h at 30°C. Termination of the reaction and all further steps are done as described for HeLa cell nuclear extracts as a source for HDAC enzymatic activity.

Recombinant human HDAC1 expressed in Hek293 cells is inhibited by Examples 3, 4, 5, 7, 8 to 11, 24, 25, 27 and 28 with an IC<sub>50</sub> ≥ 0.95 nM.

#### Cellular Histone H3 hyperacetylation assay:

To assess the cellular efficacy of a histone deacetylase inhibitor in vitro, an assay was set up in black clear-bottom 96-well plates and optimized for use on the Cellomics "ArrayScan II" platform for a quantitative calculation of histone acetylation. The protocol uses a polyclonal rabbit antibody, specifically binding to acetylated lysine 23 or, alternatively, acetylated lysine 9 + 14 of human histone H3 on fixed cells with an Alexa Fluor 488 labeled goat anti rabbit-IgG used for counterstaining (modified from Braunger et al. AACR annual conference 2003, Abstract 4556).

5x10<sup>3</sup> HeLa cervical carcinoma cells/well (ATCC CCL-2) in 200μl Dulbecco's modified Eagle's medium (DMEM) containing 10% fetal calf serum are seeded at day 1 in Packard view plates and incubated for 24h under standard cell culture conditions. On day 2, 1μl test compound (200x final concentration) is added and incubation continued for further 24h. On day 3, the culture medium is discarded and attached cells fixed for 15min at room temperature by addition of 100μl fixation buffer

(3.7% v:v formaldehyde in phosphate buffered saline / PBS). After discarding the fixation buffer and one wash with blocking solution (1% BSA, 0,3% Tween 20 in PBS), cells are permeabilized at room temperature by addition of 100µl/well permeabilization buffer (30,8 mM NaCl, 0,54 mM Na<sub>2</sub>HPO<sub>4</sub>, 0,31 mM KH<sub>2</sub>PO<sub>4</sub>, 0,1% v:v Triton X-100) for 15min at room temperature. After discarding the permeabilization buffer and washing twice with 100µl/well blocking solution at room temperature, the 1<sup>st</sup> antibody (anti-K23 histone H3 antibody, Cell Signaling No. 9674 or, alternatively, anti-K9+14 histone H3 antibody, Calbiochem No. 382158) in blocking solution (50µl/well) is added. After incubation for 1h at room temperature, the wells are washed twice at room temperature with 100µl/well blocking solution before addition of the 2<sup>nd</sup> antibody (goat-anti-rabbit Alexa Fluor 488; MoBiTec No. A-11008) in blocking solution (50µl/well). After further incubation for 1h at room temperature, wells are washed twice with 100µl/well blocking solution at room temperature. Finally, 100µl/well PBS are added and image analysis performed on the Cellomics "ArrayScan II" platform. For EC<sub>50</sub> determination, the percentage of positive cells showing nuclear fluorescence is determined and EC<sub>50</sub> calculation done from concentration-effect curves by means of non-linear regression. For calibration, a positive (reference HDAC inhibitors like SAHA or NVP LBH-589) and a negative control were included.

The histone hyperacetylating cellular potency expressed by EC<sub>50</sub> values for selected compounds according to the present invention is shown in the following table 2, in which the numbers of the compounds correspond to the numbers of the examples.

**Table 2: Induction of histone H3 hyperacetylation in HeLa cervical carcinoma cells**

Compound	EC <sub>50</sub> (µM)
1 2 3 4 7 8 9, 10 and 27	The EC <sub>50</sub> values of these listed compounds are in the range from 2.15 to 51.3
3, 9, 10 and 24	The EC <sub>50</sub> values of these listed compounds are in the range from 0.08 to 16

Cellular cytotoxicity assay:

The anti-proliferative activity of the histone deacetylase inhibitory compounds as described herein, was evaluated using the following cell lines: HeLa and HeLa-KB (cervical carcinoma), H460 (non small cell lung cancer), A549 (non-small cell lung cancer), MCF7 (breast carcinoma), MCF10A (normal, non tumorigenic breast epithelial), MDA-MB468 (breast carcinoma), MDA-MB435 (breast carcinoma), MDA-MB231 (breast carcinoma), SKBR-3 (breast carcinoma), SKOV-3 (ovarial carcinoma), A-2780 (ovarial carcinoma), RKO (colon carcinoma), HCT-15 (colon carcinoma), HCT-116 (colon carcinoma), PC3 (prostate carcinoma), BPH1 (benign prostate hyperplasia), AsPC1 (pancreatic carcinoma), Cal27 (tongue carcinoma), A-431 (vulva carcinoma), Hec1A (endometrial carcinoma), Saos-2 (osteosarcoma), U87MG (glioblastoma), WM266-4 (melanoma), K562 (chronic myeloid carcinoma), EOL1 (acute hypereosinophilic myeloid leukemia), CCRF-CEM and CCRF-CEM VCR1000 (acute lymphoblastic leukemia sensitive and resistant towards Vincristine). For quantification of cellular proliferation / living cells the Alamar Blue (Resazurin) cell viability assay was applied (O'Brien et al. Eur J Biochem 267, 5421-5426, 2000). In this assay Resazurin is reduced to the fluorescent resorufin by cellular dehydrogenase activity, correlating with viable, proliferating cells. The examples were dissolved as 20 mM solutions in dimethylsulfoxide (DMSO) and subsequently diluted in semi-logarithmic steps. Cell lines were seeded at respective density into 96 well flat bottom plates in a volume of 200  $\mu$ l per well. 24 hours after seeding 1  $\mu$ l each of the compound dilutions were added into each well of the 96 well plate. Each compound dilution was tested as quadruplicates. Wells containing untreated control cells were filled with 200  $\mu$ l DMEM medium containing 0.5% v:v DMSO. The cells were then incubated with the substances for 72 hours at 37°C in a humidified atmosphere containing 5% carbon dioxide. To determine the viability of the cells, 20  $\mu$ l of an Resazurin solution (Sigma; 90mg / l) were added. After 4 hours incubation at 37°C the fluorescence was measured at an extinction of 544 nm and an emission of 590 nm. For the calculation of the cell viability the emission value from untreated cells was set as 100% viability and the emission rates of treated cells were set in relation to the values of untreated cells. Viabilities were expressed as % values. The corresponding IC<sub>50</sub> values of the compounds for cytotoxic activity are determined from the concentration-effect curves by means of non-linear regression.

For combination experiments, examples 3, 9, 10 and 24 around the IC<sub>50</sub> concentration (as determined from the Alamar Blue assay) were tested in combination with respective anti-cancer agents Taxol, Docetaxel, 5-Fu, Irinotecan, Doxorubicin, Carboplatin, Cisplatin, Gemcitabine, Mafosfamide and Trail at variable concentrations. The concentration of examples used in these combination experiments were as follows: 0.4  $\mu$ M (ex. 3), 2.5 $\mu$ M (ex. 9), 2.3 $\mu$ M (ex. 10) and 0.25 $\mu$ M (ex. 24). A549 non-small cell lung cancer, MDA-MB468 breast cancer and HCT-166 colorectal cancer cell lines were pretreated with the examples for 4h before adding the chemotherapeutic agents or Trail and further incubation for 72h total. The IC<sub>50</sub> values of these combinations were determined from concentration-effect curves and compared to IC<sub>50</sub> values of cell treated with the anti-cancer agent only.

For determination of cell-cycle dependent cytotoxicity, the RKO exop21 cell system was applied (Schmidt et al. Oncogene 19: 2423-2429, 2000). Briefly, RKO cells with / without p21<sup>waf1</sup> expression

( $2 \times 10^4$  cells/well induced,  $6 \times 10^3$  cells/well not induced) were treated with the examples for 72h and metabolic activity quantified as described before. The expression of p21<sup>waf1</sup> was induced by treatment with Pronasterone A, causing a complete proliferation arrest of RKO cells in the G1 and G2 phases of the cell division cycle.

The anti-proliferative / cytotoxic potency expressed by IC<sub>50</sub> values for selected compounds according to the present invention is shown in the following table 3, in which the numbers of the compounds correspond to the numbers of the examples.

**Table 3: Cytotoxicity in HeLa cervical carcinoma cells**

Compound	IC <sub>50</sub> (μM)
1 2 3 4 7 8	The IC <sub>50</sub> values of these listed compounds are in the range from 0.8 to 21.6
9 to 28	The IC <sub>50</sub> values of these listed compounds are in the range from 0.07 to 5

The anti-proliferative activity of examples 3, 9, 10 and 24 is evaluated by using a broad selection of non-malignant cell lines and fully transformed malignant cancer cell lines. Mean IC<sub>50</sub> values are 0.85μM for ex. 3, 3.7μM for ex. 9, 4.6μM for ex. 10, and 0.57μM for ex. 24.

Each of the examples 3, 9, 10 and 24 is combined at about its IC<sub>50</sub> concentration with an anti-cancer agent selected from the group consisting of established chemotherapeutic and target-specific anti-cancer agents, such as, in one embodiment, with an antimitotic agent / tubulin inhibitor such as e.g. a taxane like Taxol and Docetaxel, in a further embodiment, with a pyrimidine antagonist such as e.g. 5-FU and Gemcitabine, in a further embodiment, with a topoisomerase 1 or 2 inhibitor such as e.g. camptothecin or a camptothecin analog (like Irinotecan) or an anthracycline (like Doxorubicin), in a further embodiment, with an alkylating / carbamylating agent such as e.g. Mafosfamide, in a further embodiment, with a platinum derivative such as e.g. Carboplatin and Cisplatin) or, in a further embodiment, with a death receptor agonist like the death receptor DR4/5 ligand Trail, using the mammary carcinoma model MDA-MB468, the colorectal carcinoma model HCT116 and the non-small

cell lung cancer model A549. For all chemotherapeutic agents mentioned above additive effects are noted (no significant effect of the combination on the IC<sub>50</sub> of the chemotherapeutic agent), whereas synergism is highly likely with Trail in the A549 cell line model.

By using proliferating and arrested RKO colon carcinoma cells with conditional p21<sup>waf1</sup> expression as described above the proliferation independent mode of action of examples 3, 9, 10 and 24 is shown (see table 4). Dormant, non-proliferating as well as proliferating tumor cells are hit by the examples as described herein.

**Table 4: Cell cycle independent cytotoxicity**

Compound	RKO proliferating IC <sub>50</sub> (μM)	RKO arrested (p21 <sup>waf1</sup> expressed) IC <sub>50</sub> (μM)
3, 9, 10 and 24	The IC <sub>50</sub> values of these listed compounds are in the range from 0.15 to 5.1	The IC <sub>50</sub> values of these listed compounds are in the range from 0.45 to 15

#### Breast cancer cell differentiation assay

For quantification of MDA-MB468 breast cancer cell differentiation (described by Munster et al. Canc. Res. 61(23), pp8492, 2001), 1x E6 cells were seeded in 10cm cell culture dishes and, after cultivation for 24h, treated with HDI for further 24h. Finally, cells were collected by trypsination, washed twice with PBS and resuspended in 1ml of staining solution (5μg/ml Nile Red in PBS). After incubation for at least 5min at room temperature, cells were analysed by flow cytometry on a FACS Calibur device (Ex 488nm, Em. at 530nm / FL-1 and >630nm / FL-3). From respective histograms the percentage of cells with fluorescence at 650nm (phospholipids) and 530nm+650nm (phospho- and neutral lipids) were calculated. For microscopic analysis, MDA-MB468 cells were cultivated on two-well chamber slides, treated with test compound for 24h, fixed with 1.5vol% glutaraldehyde / PBS and finally treated with staining solution. After washing with PBS, cells were analysed by fluorescence microscopy.

MDA-MB468 cells are treated with examples 3, 9, 10 and 24 at the respective IC<sub>50</sub> and 2x IC<sub>50</sub> concentrations (as determined in cytotoxicity assays) for 24h before analysis of phospholipid / neutral lipid content by Nile Red staining and flow cytometry. The percentage of differentiated cells with neutral and phospholipids as well as undifferentiated cells with phospholipids only are summarized in the table 5.

**Table 5: Induction of MDA-MB468 breast cancer cell differentiation**



Compound	Concentration ( $\mu$ M)	Neutral & phospholipids (%)	Phospholipids (%)
	control	4,5	92,6
10	2	55,5	41,6
	5	70,2	25,2
9	3	71,2	25,3
	6	64,6	27,9
3	0,6	34,6	62,6
	1,2	51,2	45,7
24	0,8	67,3	27,9
	1,6	63,6	30,7

#### Apoptosis induction

The induction of apoptosis was measured by using the cell death detection ELISA (Art. No. 1774425, Roche Biochemicals, Mannheim, Germany). A549 NSCLC cells were seeded into 96 well flat bottom plates at a density of  $3 \times 10^3$  cells/well in a total volume of 200  $\mu$ l/well. 24 hours after seeding, 1  $\mu$ l each of the compound dilutions in DMEM were added in a total volume of 200  $\mu$ l into each well. Each compound dilution was tested at least as triplicates. Wells containing untreated control cells were filled with 200  $\mu$ l DMEM containing 0.5 vol% DMSO. The cells were incubated with test compound for 48 hours at 37°C in a humidified atmosphere containing 5% carbon dioxide. As a positive control for the induction of apoptosis, cells were treated with 50  $\mu$ M Cisplatin (Gry Pharmaceuticals, Kirchzarten, Germany). Medium was then removed and the cells lysed in 200  $\mu$ l lysis buffer. After centrifugation as described by the manufacturer, 10  $\mu$ l of cell lysate was processed as described in the protocol. The degree of apoptosis was calculated as follows: The absorbance at 405 nm obtained with lysates from cells treated with 50  $\mu$ M cisplatin is set as 100 cpu (cisplatin units), while an absorbance at 405 nm of 0.0 is set as 0.0 cpu. The degree of apoptosis is expressed as cpu in relation to the value of 100 cpu reached with the lysates obtained from cells treated with 50  $\mu$ M cisplatin.

Representative apoptosis inducing potency values (expressed by cpu values) for compounds according to the present invention follows from the following table 6, in which the numbers of the compounds correspond to the numbers of the examples.

**Table 6: Apoptosis induction**

Compound	cpu @ 10μM
3, 9, 10 and 24	The cpu values of these listed compounds are in the range from 248 to 380

**Patent Claims**

1. A salt of a compound selected from  
(E)-N-hydroxy-3-(1-[4-((2-(1H-indol-2-yl)-ethyl)-methyl-amino)-methyl]-benzene sulfonyl)-1H-pyrrol-3-yl)-acrylamide,  
(E)-3-[1-(4-dimethylaminomethyl-benzenesulfonyl)-1H-pyrrol-3-yl]-N-hydroxy-acrylamide, and  
(E)-N-hydroxy-3-[1-(5-pyridin-2-yl-thiophene-2-sulfonyl)-1H-pyrrol-3-yl]-acrylamide  
with hydrochloric acid, or a hydrate thereof or a crystalline form of this salt or hydrate.
2. A salt of (E)-3-[1-(4-dimethylaminomethyl-benzenesulfonyl)-1H-pyrrol-3-yl]-N-hydroxy-acrylamide  
with hydrochloric acid, or a hydrate thereof.
3. The compound according to claim 1 or 2 being in crystalline form and having from about 0.1 to  
about 1.9 equivalent hydrochloric acid with respect to the free base.
4. A crystalline hydrochloride salt of (E)-3-[1-(4-dimethylaminomethyl-benzenesulfonyl)-1H-pyrrol-3-yl]-N-hydroxy-acrylamide, a hydrate or a polymorph thereof.
5. A form A polymorph according to claim 4 having a X-ray diffraction pattern, which comprises  
peaks at about 5.8, 11.5, 15.0, 17.1, 17.4, 17.5, 18.2, 19.9, 20.1, 20.6, 21.3, 21.5, 23.2, 24.1,  
25.0, 25.4, 25.8, 26.9, 27.5, 28.5, 29.1, 30.1, 30.2, 30.8 and 32.3 in  $2\theta$ ; when the pattern is  
obtained using Cu K $\alpha$  radiation.
6. A form B polymorph according to claim 4 having a X-ray diffraction pattern, which comprises  
peaks at about 10.1, 17.0, 17.7, 17.9, 20.3, 20.8, 21.1, 22.7, 23.1, 24.1, 26.2, 26.8, 27.9, 28.9  
and 34.5 in  $2\theta$ ; when the pattern is obtained using Cu K $\alpha$  radiation.
7. A salt of (E)-N-hydroxy-3-[1-(5-pyridin-2-yl-thiophene-2-sulfonyl)-1H-pyrrol-3-yl]-acrylamide with  
hydrochloric acid, or a hydrate thereof.
8. The compound according to any of the claims 1 to 7 having from about 0.8 to about 1.2  
equivalent hydrochloride with respect to the free base.
9. The compound according to any of the claims 1 to 7 having about one equivalent hydrochloride  
with respect to the free base.
10. The compound according to any of the preceding claims being in substantially pure form.
11. The compound according to any of the preceding claims being substantially devoid of  
amorphous forms thereof.
12. The compound according to any of the claims 1 to 11 in solid dosage form.
13. The compound according to any of the claims 1 to 11 in a pharmaceutically acceptable form.
14. A process for preparing a compound according to claim 4 comprising the step of crystallization  
or recrystallization of any form or mixtures of any forms of (E)-3-[1-(4-dimethylaminomethyl-  
benzenesulfonyl)-1H-pyrrol-3-yl]-N-hydroxy-acrylamide with hydrochloric acid in a solution  
comprising organic solvent or mixture of organic solvents, or mixtures thereof with water, or  
water.
15. A compound according to any of the claims 1 to 13 for use in the treatment of diseases.
16. A pharmaceutical composition comprising a compound according to any of the claims 1 to 13  
together with customary pharmaceutical diluents, excipients and/or carriers.

17. Use of a compound according to any of the claims 1 to 13 for the manufacture of pharmaceutical compositions for treating, preventing or ameliorating benign or malignant neoplasia, such as e.g. cancer.
18. A method for treating, preventing or ameliorating hyperproliferative diseases of benign or malignant behaviour and/or disorders responsive to induction of apoptosis, such as, for example, benign or malignant neoplasia, e.g. cancer, in a patient comprising to said patient a therapeutically effective and tolerable amount of a compound according to any of the claims 1 to 13.
19. A method for treating diseases responsive or sensitive to inhibition of histone deacetylase activity in a patient comprising administering to said patient a therapeutically effective amount of a compound according to any of the claims 1 to 13.
20. A combination comprising  
a first active ingredient, which is at least one compound according to any of the claims 1 to 13, and  
a second active ingredient, which is at least one anti-cancer agent selected from the group consisting of chemotherapeutic anti-cancer agents and target-specific anti-cancer agents, for separate, sequential, simultaneous, concurrent or chronologically staggered use in therapy, such as e.g. in therapy of benign or malignant neoplasia, e.g. cancer.
21. A method for treating, preventing or ameliorating hyperproliferative diseases and/or disorders responsive to induction of apoptosis, such as, for example, benign or malignant neoplasia, e.g. cancer, in a patient comprising administering separately, simultaneously, concurrently, sequentially or chronologically staggered to said patient in need thereof  
an amount of a first active compound, which is a compound according to any of the claims 1 to 13, and  
an amount of at least one second active compound, said second active compound being an anti-cancer agent selected from the group consisting of chemotherapeutic anti-cancer agents and target-specific anti-cancer agents,  
wherein the amounts of the first active compound and said second active compound result in a therapeutic effect.
22. The combination or method according to claim 20 or 21, in which said chemotherapeutic anti-cancer agents are selected from (i) alkylating/carbamylating agents including Cyclophosphamid, Ifosfamid, Thiotepa, Melphalan and chloroethylnitrosourea; (ii) platinum derivatives including cis-platin, oxaliplatin, satraplatin and carboplatin; (iii) antimitotic agents / tubulin inhibitors including vinca alkaloids, such as e.g. vincristine, vinblastine or vinorelbine, taxanes, such as e.g. Paclitaxel, Docetaxel and analogs as well as formulations and conjugates thereof, and epothilones, such as e.g. Epothilone B, Azaepothilone or ZK-EPO; (iv) topoisomerase inhibitors including anthracyclines, such as e.g. Doxorubicin, epipodophyllotoxines, such as e.g. Etoposide, and camptothecin and camptothecin analogs, such as e.g. Irinotecan or Topotecan; (v) pyrimidine antagonists including 5-fluorouracil, Capecitabine, Arabinosylcytosine / Cytarabin

- and Gemcitabine; (vi) purin antagonists including 6-mercaptopurine, 6-thioguanine and fludarabine; and (vii) folic acid antagonists including methotrexate and pemetrexed.
23. The combination or method according to claim 20, 21 or 22, in which said target-specific anti-cancer agents are selected from (i) kinase inhibitors including Imatinib, ZD-1839 / Gefitinib, BAY43-9006 / Sorafenib, SU11248 / Sunitinib, OSI-774 / Erlotinib, Dasatinib, Lapatinib, Vatalanib, Vandetanib and Pazopanib; (ii) proteasome inhibitors including PS-341 / Bortezomib; (iii) histone deacetylase inhibitors including SAHA, PXD101, MS275, MGCD0103, Depsiptide / FK228, NVP-LBH589, LAQ-824, Valproic acid (VPA) and butyrates; (iv) heat shock protein 90 inhibitors including 17-allylaminogeldanamycin (17-AAG); (v) vascular targeting agents (VAT) including combretastatin A4 phosphate and AVE8062 / AC7700, and anti-angiogenic drugs including VEGF antibodies, such as e.g. Bevacizumab, and KDR tyrosine kinase inhibitors, such as e.g. PTK787 / ZK222584 (Vatalanib), Vandetanib or Pazopanib; (vi) monoclonal antibodies including Trastuzumab, Rituximab, Alemtuzumab, Tositumab, C225/ Cetuximab, Bevacizumab and Panitumumab as well as mutants and conjugates of monoclonal antibodies, such as e.g. Gemtuzumab ozogamicin or Ibritumomab tiuxetan, and antibody fragments; (vii) oligonucleotide based therapeutics including G-3139 / Oblimersen; (viii) Toll-like receptor / TLR 9 agonists including Promune®, TLR 7 agonists like Imiquimod and Isatoribine and analogues thereof, or TLR 7/8 agonists including Resiquimod as well as immunostimulatory RNA as TLR 7/8 agonists; (ix) protease inhibitors (x) hormonal therapeutics including anti-estrogens, such as e.g. Tamoxifen or Raloxifen, anti-androgens, such as e.g. Flutamide or Casodex, LHRH analogs, such as e.g. Luprolide, Goserelin or Triptorelin, and aromatase inhibitors; bleomycin; retinoids including all-trans retinoic acid (ATRA); DNA methyltransferase inhibitors including the 2-deoxycytidine derivative Decitabine and 5-Azacytidine; alanosine; cytokines including interleukin-2; interferons including interferon  $\alpha$ 2 and interferon- $\gamma$ ; and death receptor agonists including TRAIL, DR4/5 agonistic antibodies, FasL and TNF-R agonists, such as e.g. TRAIL receptor agonists like mapatumumab or lexatumumab.
24. The combination or method according to claim 20, 21 or 22, in which said target-specific anti-cancer agents are selected from death receptor agonists including TRAIL, DR4/5 agonistic antibodies, FasL and TNF-R agonists, such as e.g. TRAIL receptor agonists like mapatumumab or lexatumumab.
25. The use, method or combination according to any of the claims 17, 18, 20 and 21, in which said cancer is selected from the group consisting of  
cancer of the breast, bladder, bone, brain, central and peripheral nervous system, colon, endocrine glands, esophagus, endometrium, germ cells, head and neck, kidney, liver, lung, larynx and hypopharynx, mesothelioma, sarcoma, ovary, pancreas, prostate, rectum, renal, small intestine, soft tissue, testis, stomach, skin, ureter, vagina and vulva;  
inherited cancers, retinoblastoma and Wilms tumor;  
leukemia, lymphoma, non-Hodgkins disease, chronic and acute myeloid leukaemia, acute lymphoblastic leukemia, Hodgkins disease, multiple myeloma and T-cell lymphoma;

**- 97 -**

myelodysplastic syndrome, plasma cell neoplasia, paraneoplastic syndromes, cancers of unknown primary site and AIDS related malignancies.

## Drawings

Fig. Aa:

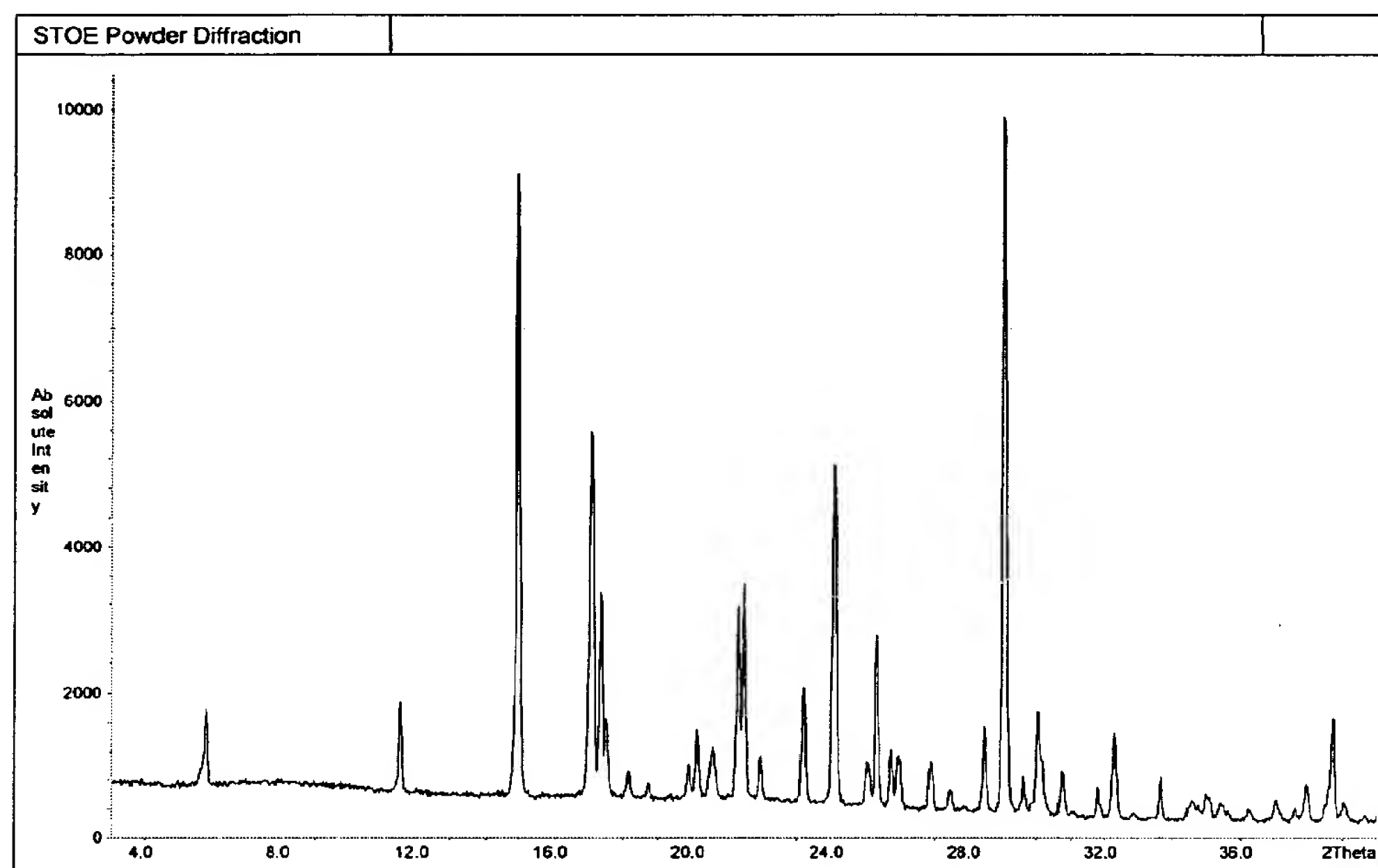


Fig. Ab:

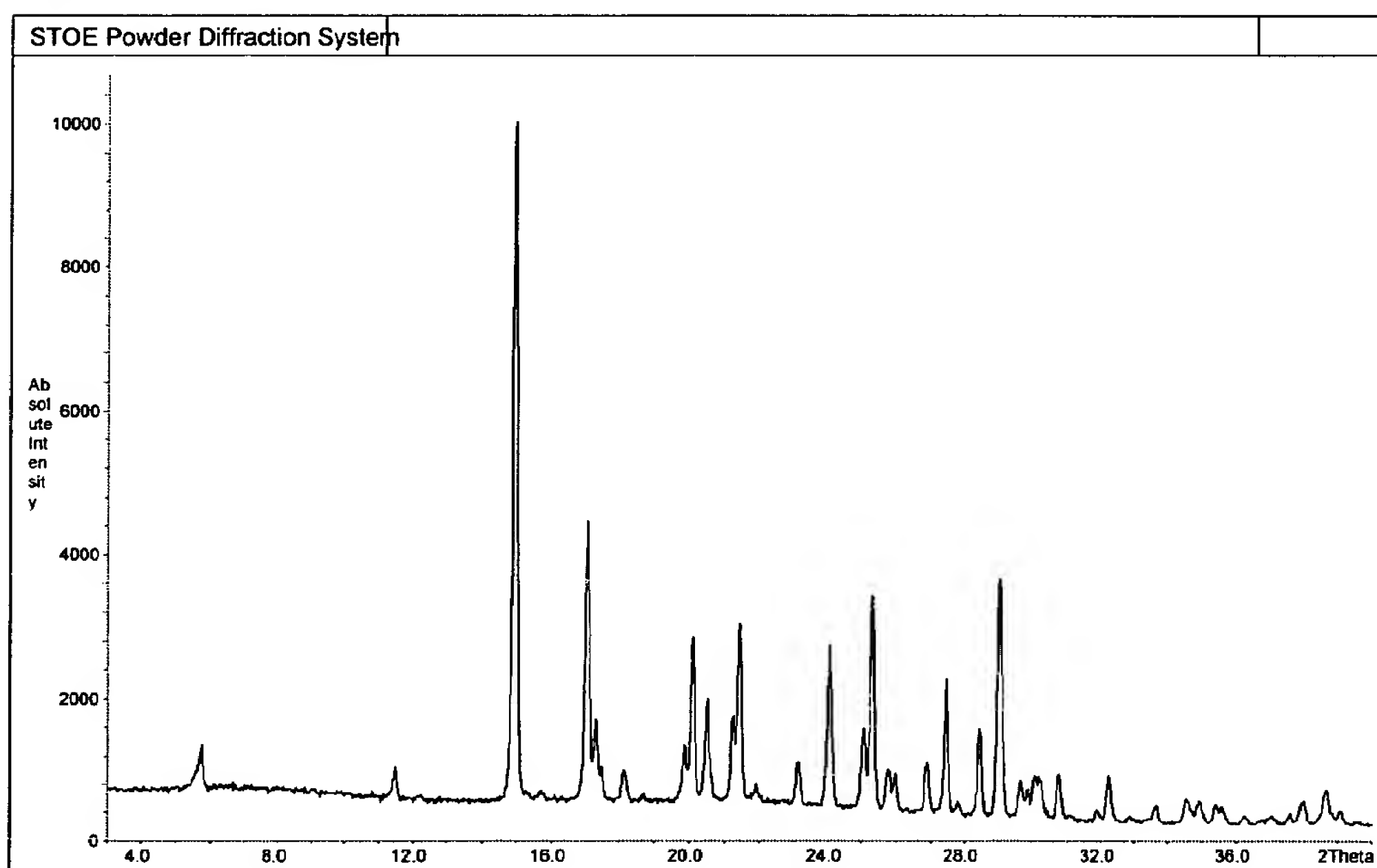
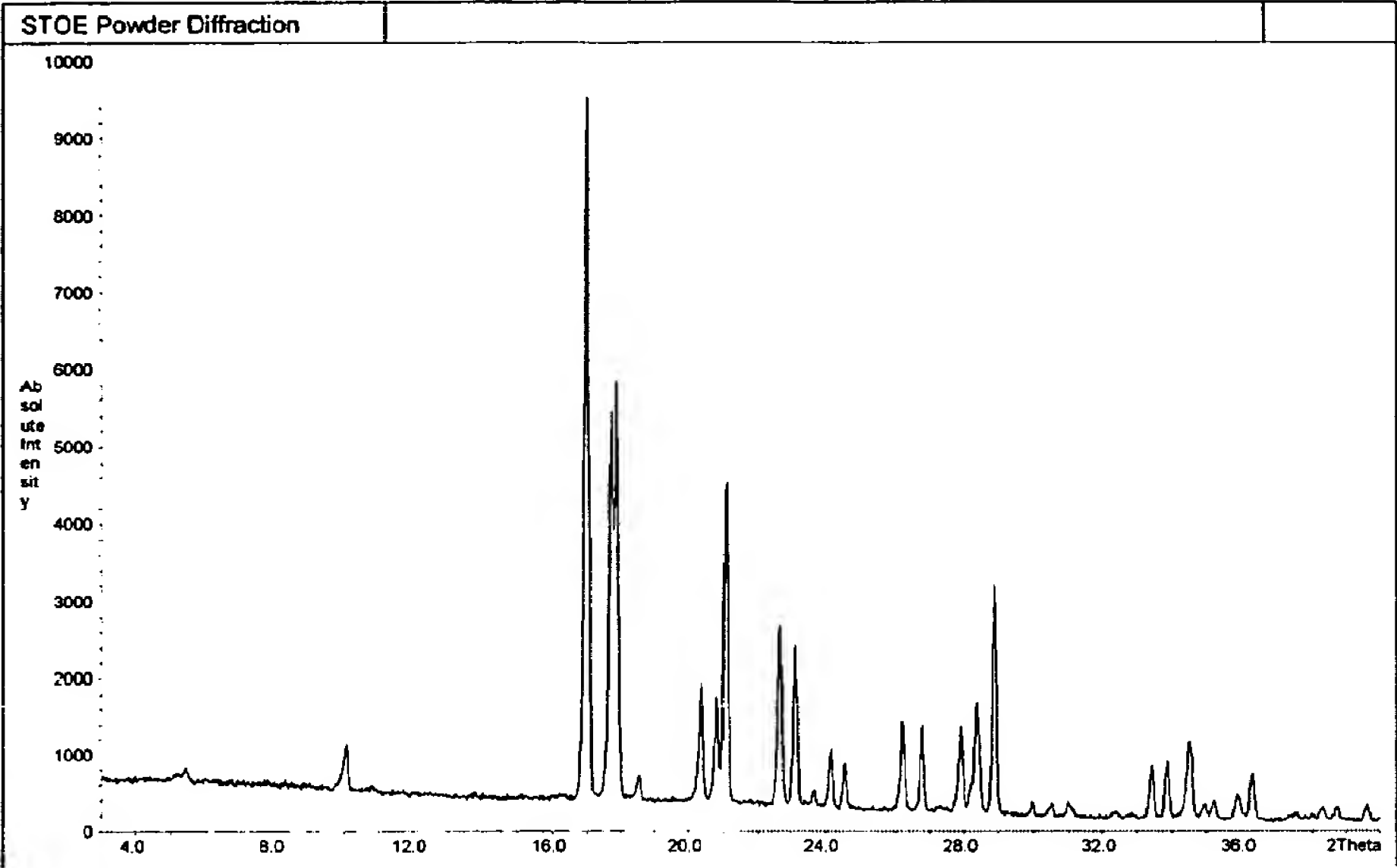


Fig. B:





# INTERNATIONAL SEARCH REPORT

International application No  
PCT/EP2006/066189

**A. CLASSIFICATION OF SUBJECT MATTER**  
INV. C07D207/48 A61K31/40

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)  
EPO-Internal, CHEM ABS Data, WPI Data, BIOSIS

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, P	WO 2005/087724 A (ALTANA PHARMA AG; MAIER, THOMAS; BECKERS, THOMAS; BAER, THOMAS; GIMMNI) 22 September 2005 (2005-09-22) examples 9,10,24 page 14, paragraph 7 ----- -/--	1,15

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

\* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance  
"E" earlier document but published on or after the international filing date  
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)  
"O" document referring to an oral disclosure, use, exhibition or other means  
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention  
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone  
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.  
"&" document member of the same patent family

Date of the actual completion of the international search

20 November 2006

Date of mailing of the international search report

28/11/2006

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Authorized officer

Fanni, Stefano

## INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2006/066189

## C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>MAI ET AL: "3-(4-Aroyl-1-methyl-1H-2-pyrrolyl)-N-hydroxy-2-propenamides as a New Class of Synthetic Histone Deacetylase Inhibitors. 2. Effect of Pyrrole-C2 and/or -C4 Substitutions on Biological Activity" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 47, no. 5, 2004, pages 1098-1109, XP002292253 ISSN: 0022-2623 cited in the application the whole document</p> <p>-----</p>	1,15
A	<p>BOUCHAIN G ET AL: "Development of Potential Antitumor Agents. Synthesis and Biological Evaluation of a New Set of Sulfonamide Derivatives as Histone Deacetylase Inhibitors" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 46, 2003, pages 820-830, XP002278212 ISSN: 0022-2623 cited in the application the whole document</p> <p>-----</p>	1,15
A	<p>REMISZEWSKI S W: "RECENT ADVANCES IN THE DISCOVERY OF SMALL MOLECULE HISTONE DEACETYLASE INHIBITORS" CURRENT OPINION IN DRUG DISCOVERY AND DEVELOPMENT, CURRENT DRUGS, LONDON, GB, vol. 5, no. 4, July 2002 (2002-07), pages 487-499, XP008025513 ISSN: 1367-6733 cited in the application the whole document</p> <p>-----</p>	1,15

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/EP2006/066189

## Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Although claims 18,19,21-25 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

### Information on patent family members

PCT/EP2006/066189

Form PCT/ISA/210 (patent family annex) (April 2005)